D'Antonio Francesco (Orcid ID: 0000-0002-7546-8025)
Prasad Smriti (Orcid ID: 0000-0003-2329-4470)
Eltaweel Nashwa (Orcid ID: 0000-0003-0219-3283)
Khalil Asma (Orcid ID: 0000-0003-2802-7670)

Selective fetal growth restriction in dichorionic diamniotic twin pregnancies: systematic review and meta-analysis of maternal and perinatal outcomes

F. D'Antonio[1], S. Prasad[2,3,4], L. Masciullo[2,4], N. Eltaweel[5] and A. Khalil[2,3,4,6]

[1]Center for Fetal Care and High-Risk Pregnancy, University of Chieti, Chieti, Italy
[2]Fetal Medicine Unit, St George's University Hospital, London, UK
[3]Vascular Biology Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, London, UK
[4]Twins Trust Centre for Research and Clinical Excellence, St George's University Hospital, St George's University of London, London, UK
[5]Division of Biomedical Science, Warwick Medical School, University of Warwick, University Hospital of Coventry and Warwickshire, Coventry, UK
[6]Fetal Medicine Unit, Liverpool Women's Hospital, University of Liverpool, Liverpool, UK

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Corresponding Author:
Prof. Asma Khalil
Fetal Medicine Unit, Department of Obstetrics and Gynaecology
St. George's University Hospitals NHS Foundation Trust
Blackshaw Road
London SW17 0QT, UK
E-mail: akhalil@sgul.ac.uk

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Contribution

What are the novel findings of this work?

When compared with uncomplicated dichorionic twin pregnancies, selective fetal growth restriction in dichorionic twin pregnancies increased the chance of intrauterine death, (5 fold higher) as well as neonatal morbidity and admission to neonatal unit (3 fold higher). The study presents estimates of adverse outcomes in these complicated pregnancies

What are the clinical implications of this work?

Dichorionic twin pregnancies with fetal growth restriction are at high risk of perinatal mortality and morbidity. The findings are pertinent in the counselling and management of complicated twin pregnancies, in particular fetal growth restriction in dichorionic twin pregnancies. Twin-specific, rather than singletons, outcome data should be used.

ABSTRACT

Objectives: Most of the published literature has focused on selective fetal growth restriction (sFGR) in monochorionic twin pregnancies. National and international guidelines have proposed that the management of sFGR in dichorionic twin pregnancies should be similar to that of singletons ignoring the inherent differences between multiple and singleton pregnancies and the added complexity of, as well as the impact of iatrogenic prematurity on the normally growing co-twin.

The aim of this systematic review was to report the outcomes of dichorionic diamniotic (DCDA) twin pregnancies complicated by sFGR.

Methods: Medline, Embase and Cochrane databases were searched. The inclusion criteria were DCDA twin pregnancies complicated by sFGR. The outcomes explored were intra-uterine (IUD), neonatal (NND), and perinatal death (PND), survival of at least one and both twins, preterm birth (PTB) birth (either spontaneous or iatrogenic) prior to 37, 34, 32 and 28 weeks of gestation, pre-eclampsia (PE), a composite score of perinatal morbidity, neurological, respiratory, infectious, morbidity, Apgar score <7 at 5 minutes, necrotizing enterocolitis, retinopathy of prematurity, admission to neonatal intensive care unit (NICU). Random effect meta-analyses of proportion and risk were used to analyse the data. PND death was computed only in studies reporting both IUD and NND. Furthermore, we planned sub-group analyses according to gestational age at diagnosis and Doppler status.

Results: Thirteen studies (1339 pregnancies complicated and 6316 non complicated by sFGR) were included. IUD occurred in 2.6% (95% CI 1.1-4.7) of DCDA pregnancies with and in 0.58% (95% CI 0.3-9.7) of those non complicated by sFGR, while the corresponding figures for PND were 5.2% (95% CI 3.5-7.3) and 1.7% (95% CI 0.1-5.7). PTB< 37 weeks, either spontaneous or iatrogenic, complicated 84.1% (95% CI 55.6-99.2) of pregnancies with and 69.1% (95% CI 45.4-88.4) without sFGR, while the corresponding figures for PTB <34, <32 and <28 were 18.4% (95% CI 4.4-38.9), 13.0% (95% CI 9.5-17.1) and 1.5% (95% CI 0.6-2.3) in pregnancies complicated and 10.2% (95% CI 3.1-20.7), 7.8% (95% CI 6.8-8.9) and 1.8% (95% CI 1.3-2.4) in those non-complicated by sFGR. PE complicated 19.9% (95% CI 12.4-28.6) of pregnancies with and 12.8% (95% CI 10.4-15.4) of those with no sFGR. Composite morbidity occurred in 28.2% (95% CI 7.8-55,1) of twins with and 13.9% (95% 6.5-23.5) of those without sFGR. When stratifying the risk of morbidity according to the sFGR status within a twin pair, this occurred in 39.0% (95% CI 11.1-71.5) and in 29.9% (95% CI 3.5-65.0) with an OR of 1.91 (95% CI 1.7-3.1). At risk analysis, DCDA pregnancies complicated by sFGR had

a significantly higher risk of IUD (OR: 5.23, 95% CI 3.2-8.6) and composite morbidity or admission to NICU compared to those not affected (OR of 3.22, 95% CI 1.85-5.60), while there was no difference in the risk of PTB <34 weeks of gestation (p=0.220) and PE (p=0.465).

Conclusion: DCDA twin pregnancies complicated by sFGR are at high risk of perinatal mortality and morbidity. The findings are pertinent in the counselling and management of complicated twin pregnancies, where twin-specific, rather than singletons, outcome data should be used.

INTRODUCTION

Twin pregnancies are at an increased risk of perinatal morbidity and mortality, primarily due to preterm birth and fetal growth restriction[1-9] According to the recent Delphi consensus, selective growth restriction (sFGR) in DCDA twin pregnancies is defined as either one solitary parameter (estimated fetal weight (EFW) of one twin < 3rd centile) or at least two out of three contributory parameters (EFW of one twin < 10th centile, EFW discordance of ≥ 25%, and umbilical artery pulsatility index of the smaller twin > 95th centile).[10]

Growth restriction in twin pregnancies has been established as an independent predictor of adverse perinatal outcomes.[11-15] In MCDA twin pregnancies, sFGR is further stratified according to the hemodynamic pattern of the end-diastolic flow (EDF) in the umbilical artery (UA) of the smaller fetus into types I, II and III, with type II and III being complicated by a higher risk of perinatal mortality and morbidity.[16-18] Conversely, there is less evidence on the actual risks and perinatal outcomes of sFGR in DCDA twin pregnancies. sFGR in MCDA twin pregnancies is attributed to unequal sharing of the single placenta, while in DCDA twin pregnancies with sFGR, the most likely etiology is deemed to be uteroplacental insufficiency.[6]

Guidelines on the management of DCDA twin pregnancies complicated by sFGR is to manage them in line with growth-restricted singletons.[16] However, the prognostic value of abnormal fetal Dopplers may not have the same significance for growth-restricted twins as for growth-restricted singletons and should be considered when decisions for early delivery are taken.[19,20]

The literature on the natural history of DCDA twin pregnancies is limited by variable diagnostic criteria of sFGR, small sample size of published studies, heterogeneity in outcome assessment and reporting, gestational age (GA) at diagnosis and type of prenatal follow-up. The magnitude of adverse perinatal outcomes in DCDA twin pregnancies is perceived to be lower than in MCDA twin pregnancies. However, the management of DCDA twin pregnancies complicated by sFGR remains challenging. With this background, the main aim of this systematic review and meta-analysis of the available literature was to study the maternal and perinatal outcomes in DCDA twin pregnancies complicated by sFGR.

METHODS

Protocol, information sources and literature search

This review was performed according to an a-priori designed protocol and recommended for systematic reviews and meta-analysis[21,22]. Medline and Embase databases were searched electronically on 28th April 2022, followed by an update on 17th August 2022, utilizing a combination of relevant medical subject heading (MeSH) terms, key words, and word variants for "growth restriction", "twin pregnancies", "ultrasound" and "outcome" (Supplementary Table 1). The search and selection criteria were restricted to the English language. Reference lists of relevant articles and reviews were hand searched for additional reports. Prisma guidelines were followed. The study was registered with the PROSPERO database (registration number: CRD42022361648).

Outcomes measures, study selection and data collection

The inclusion criteria were DCDA twin pregnancies complicated by sFGR according to the recently published Delphi consensus[10] as the presence of at least either one solitary parameter (EFW of one twin <3rd centile) or two out of three contributory parameters (EFW of one twin < 10th centile, , EFW discordance ≥25%, and umbilical artery pulsatility index of the smaller twin >95th centile), or, in studies published before this consensus paper, as EFW, birthweight (BW) or abdominal circumference <10th percentile with EFW or BW >20% or 25%. The outcomes explored were:

- Intra-uterine death (IUD), defined as fetal loss beyond 20 weeks of gestation
- Neonatal death (NND), defined as death until 28 days from birth
- Perinatal death (PND), defined as the sum of IUD and NND
- Survival of at least one twin
- Survival of both twins
- Preterm birth (either spontaneous or iatrogenic) prior to 37, 34, 32 and 28 weeks of gestation
- Pre-eclampsia (PE), defined as the new onset of hypertension and proteinuria or the new onset of hypertension and significant end-organ dysfunction with or without proteinuria after 20 weeks of gestation or postpartum in a previously normotensive patient
- Composite perinatal morbidity, defined as the incidence of either respiratory, neurological, infectious morbidity or admission to neonatal intensive care unit (NICU)

- Neurological morbidity, defined as the incidence of intra-ventricular hemorrhage (grade III and IV) or periventricular leukomalacia (grade II)
- Respiratory morbidity, defined as the occurrence of respiratory distress syndrome or need for mechanical ventilation
- Infectious morbidity defined as the occurrence of neonatal sepsis
- Apgar score < 7 at 5 minutes
- Necrotizing enterocolitis, ischemic necrosis of the intestinal mucosa, which is associated with severe inflammation, invasion of enteric gas forming organisms, and dissection of gas into the bowel wall and portal venous system
- Retinopathy of prematurity, defined as a developmental vascular proliferative disorder that occurs in the retina with incomplete retinal vascularization
- Admission to the neonatal intensive care unit
- Furthermore, we computed a composite score of perinatal morbidity, defined as the occurrence of either respiratory, neurological, or infectious morbidity)

All these outcomes were explored in the overall population of twin pregnancies complicated and in those not complicated by sFGR. Furthermore, we planned sub-group analyses according to GA at diagnosis and Doppler status. Perinatal death was computed only in studies reporting both IUD and NND.

Only studies reporting the outcome of DCDA twin pregnancies complicated and, when reported, in those not complicated by sFGR were considered suitable for inclusion in the present review. Studies reporting the incidence of the different explored outcomes in DCDA twin pregnancies with EFW or BW discordance without stating that the pregnancy was affected by sFGR were excluded. Studies including cases affected by sFGR in MCDA, monochorionic monoamniotic twin pregnancies, structural or chromosomal anomalies and those from which data could not be extrapolated were excluded. Studies published before 2000 were also excluded, as we considered that advances in prenatal imaging techniques, and improvements in the diagnosis and treatment of multiple pregnancies make them less relevant. Only full-text articles were considered eligible for inclusion; case reports, conference abstracts, and case series with fewer than 5 cases were excluded to avoid publication bias.

Two authors (SP, LM) reviewed all abstracts independently with the use of Covidence systematic review software (version 2, Veritas Health Innovation, Melbourne, VIC, Australia). Agreement regarding potential relevance was reached by consensus. Full-text copies of those papers were obtained, and two reviewers (SP, FD) independently extracted relevant data

regarding study characteristics and pregnancy outcomes. Inconsistencies were discussed by the reviewers and a consensus was reached or through a discussion with a third author (AK). If more than one study was published for the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations.

Quality assessment, risk of bias and statistical analysis

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS) for case-control and cohort studies. According to NOS, each study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of the outcome of interest. Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the demonstration that the outcome of interest was not present at the start of the 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.[23] A maximum of two stars can be given for Comparability.

First, we planned to report the incidence of each explored outcome in DCDA twin pregnancies complicated and in those not complicated by sFGR. We used random-effect meta-analyses to combine data and results were reported as pooled proportions with their 95% confidence intervals (CI). For the purpose of the analysis, the denominator was represented by the number of twins per each group for the computation of survivors and morbidity, while the number of pregnancies for the assessment of PTB, preeclampsia and the presence of at least one and two survivors. Then we aimed to compare the risk of each explored outcome in DCDA pregnancies complicated compared to those non-complicated by sFGR, including only studies in which pregnancies with sFGR were compared with a matched population of those with no sFGR. Unfortunately, a comprehensive pooled risk assessment was not possible for all the explored outcomes in view of the very small number of included studies per each analysis and even smaller number of events. Therefore, we performed four meta-analyses comparing the risk of the following outcomes in pregnancies complicated compared to those not complicated by sFGR:

- Overall mortality, defined as the occurrence of either IUD, NND or PND
- Preeclampsia

- PTB prior to 37 weeks of gestation
- Overall morbidity, defined as the occurrence of composite morbidity or admission to NICU

Finally, we report the risk of overall mortality and morbidity in the larger compared to the smaller twin. For the purpose of these analyses, we used random-effect meta-analyses reporting the results as odd ratios (ORs) with their 95% CI.

Between-study heterogeneity was explored using the I^2 statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, whereas I^2 values of ≥50% indicate a substantial level of heterogeneity.[24] All analyses were performed using StatsDirect Statistical Software (StatsDirect Ltd Cambridge, United Kingdom).

Funnel plots displaying the outcome rate from individual studies versus their precision (1/standard error) were carried out with an exploratory aim.[25] Tests for funnel plot asymmetry were not used when the total number of publications included for each outcome was less than ten.[26] In this case, the power of the tests is too low to distinguish chance from real asymmetry.

RESULTS

Study selection and characteristics

The literature search identified 3485 records, with additional 7 records identified through other sources. After removing duplicates and screening the abstracts, 41 full articles were assessed with respect to their eligibility for inclusion and 13 studies[27-39] were included in the meta-analysis (Table 1, Figure 1, Supplementary Table 2). These 13 studies included (after removing the studies including overlapped cases) 1339 complicated and 6316 non complicated by sFGR. The results of the quality assessment of the included studies using NOS scale tool are presented in Table 2. 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. Their major limitations were the retrospective design, heterogeneity in the outcomes observed and lack of stratification of the analysis according to the GA at diagnosis, severity of FGR, Doppler status and presence of maternal comorbidities.

Synthesis of the results

IUD occurred in 2.6% (95% CI 1.1-4.7; 63/1912 fetuses, six studies) of DCDA twin pregnancies with and in 0.58% (95% CI 0.3-9.7; 31/6728 fetuses, four studies) of those non-complicated by sFGR, while the corresponding figures for NND were 1.52% (95% CI 0.8-2.4, 18/1404, I^2: 18.8%, seven studies) and 2.17% (95% 0.1-6.6; 26/4770, I^2: 901.1%, three studies). PND occurred in 5.21% (95% CI 3.5-7.3; I^2: 34.7%, 62/1126, four studies) of pregnancies with and in 1.74% (95% CI 0.1-5.7; 36/4660; I^2: 89.7%, two studies) of those without sFGR. When reporting the individual occurrence of perinatal loss, this occurred in 3.00% (95% CI 1.8-4.5, 27/888, five studies) of growth restricted fetuses and in 1.64% (95% CI 0.9-2.6, 13/888, five studies) of appropriately grown twin with an OR of 2.11 (95% CI 1.07-4.00; p= 0.004, I^2: 0%. Survival of at least one twin was observed in 99.8% (95% CI 99.0-99.9, I^2: 0%, 252/293 pregnancies, four studies) in pregnancies with and 99.5% (95% CI 97.7-99.8, I^2: 36.5%, 2302/2330 pregnancies, two studies), while the corresponding figures for survival of both twins were 92.3% (95% CI 85-0-97.3) and 98.7 (95% CI 98.2-99.1).

PTB <37 weeks, either spontaneous or iatrogenic, complicated 84.1% (95% CI 55.6-99.2; I^2: 98%, 467/628 pregnancies, five studies) of pregnancies with and 69.1% (95% CI 45.4-88.4; I^2: 99.1%,1875/3010; two studies) without sFGR, while the corresponding figures for PTB <34, <32 and <28 weeks were 18.4% (95% CI 4.4-38.9), 13.0% (95% CI 9.5-17.1) and 1.5% (95% CI 0.6-2.3) in pregnancies complicated and 10.2% (95% CI 3.1-20.7), 7.8 (95% CI 6.8-8.9)

and 1.8% (95% CI 1.3-2.4) in those non complicated by sFGR. Sub-group analyses considering the different indications for delivery (spontaneous vs iatrogenic) could not be computed in view of the lack of information from the original studies. Preeclampsia complicated 19.9% (95% CI 12.4-28.6) of pregnancies with and 12.8% (95% CI 10.4-15.4) of those with no sFGR.

Composite morbidity occurred in 28.2% (95% CI 7.8-55,1; I2: 99.1%, 402/1546 twins, six studies) of twins with and 13.9% (95% 6.5-23.5; I^2: 0% 47/2604, two studies) of those without sFGR. When stratifying the risk of morbidity according to the sFGR status within a twin pair, this occurred in 39.0% (95% CI 11.1-71.5) and in 29.9% (95% CI 3.5-65.0) with an OR of 1.91 (95% CI 1.7-3.1; I2: 60.7, p=0.012, 94/219 vs 72/218; four studies). Apgar score <7 at 5 minutes was observed in 1.06% (95% CI 0.03-3.5: 18/1105, three studies) of twins from pregnancies with sFGR while there was not corresponding figure for those without sFGR. Respiratory morbidity was reported in 18.3% (95% CI 3.3-41.7; I^2: 97%, 87/759 twins, four studies) twins from pregnancies complicated and in 9.88% (95% CI 8.1-11.8; I^2: 14.4%, 15/1555 twins, two studies, while no pooled data synthesis on neurologic and infectious morbidity could be performed. Finally, 39.7% (95% CI 17.4-64.6; I^2: 98%, 378/978 twins, five studies) of twins from pregnancies complicated and 16.3% (955 CI 8.0-26.7; I^2: 0%, 411/2045 twins, two studies) from those non-complicated by sFGR were admitted to NICU.

We could not perform sub-group analyses according to GA at diagnosis, Doppler status and severity of sFGR because the original publications did not report this information.

Computation of ORs was also affected by the very small number of cross-matched studies and even smaller number of events which precluded a comprehensive pooled data analysis. DCDA twin pregnancies complicated by sFGR had a significantly higher risk of IUD (OR: 5.23, 95% CI 3.2-8.6; p<0.001, I^2: 81.8% four studies) (Figure 2) and composite morbidity or admission to NICU compared to those not affected (OR: 3.22, 95% CI 1.85-5.60, p=0.012; I^2: 76.2%, three studies) (Figure 3), while there was no significant difference in the risk of PTB <34 weeks of gestation (p=0.220) and preeclampsia (p=0.465). Finally, the risk of overall mortality (OR: 2.07, 95% CI 1.04-4.10, p= 0.037, I^2: 0%, 27/888 vs 13/888, five studies) was higher in the smaller compared to larger twin while there was no difference in that of morbidity (p=0.475, OR: 1.47, 95% CI 0.55-3.93, I^2: 65%, 77/160 vs 66/160, three studies).

DISCUSSION

Summary of the main findings

The findings from this meta-analysis provide estimates of perinatal mortality and morbidity in DCDA twin pregnancies complicated by sFGR, and quantify this excess risk compared to DCDA twin pregnancies without sFGR. Perinatal death occurred in 5.1% of these pregnancies, while composite morbidity in 28%; about 40% of twins from pregnancies with sFGR were admitted to NICU. The risk assessment was affected by the smaller number of included studies compared to the main analysis. Overall, we reported that DCDA twin pregnancies complicated by sFGR were at five times higher risk of perinatal loss and three times higher risk of composite morbidity compared to DCDA twins not complicated by sFGR. In our review, the difference in the occurrence of PE and PTB <34 weeks was not significantly different between DCDA twin pregnancies with and without sFGR.

Strengths and limitations

This is, to the best of our knowledge, the first systematic review exploring the outcome of DCDA twin pregnancies complicated by sFGR. Thorough literature search and multitude of outcomes explored represent the main strengths of this review. Retrospective non-randomized design of the included studies, their small sample size, variable definitions of sFGR, dissimilarity in the prenatal management of pregnancies complicated by sFGR and lack of stratification of the analysis according to the degree of fetal smallness, Doppler status, and gestational age at diagnosis among the others represent its main weakness. Assessment of the potential publication bias was also problematic because of the nature of the outcomes evaluated (outcome rates, with the left-side limited to a value of zero), which limits the reliability of funnel plots, and because of the scarce number of individual studies, which strongly limits the reliability of formal tests. However, despite its limitation, the present review represents the most comprehensive up to date appraisal of the published literature on the outcomes of DCDA twin pregnancies complicated by sFGR.

Interpretation of findings

The definition, assessment, and management of sFGR in DCDA twin pregnancies have been inconsistent among the different national and international clinical practice guidelines. The American College of Obstetricians and Gynecologists (ACOG) does not specifically define sFGR but considers a difference of 15–25% in the EFW to constitute discordant fetal growth.[40]

Conversely, the ISUOG guideline on twin pregnancies defines sFGR as a condition in which the EFW of one fetus is below the 10th centile and the intertwin EFW discordance is equal or greater than 25%, but states that EFW discordance greater than 20% should prompt increased fetal surveillance.[16] Our findings provide evidence that the incidence of perinatal mortality and morbidity in DCDA twin pregnancies complicated by sFGR is higher than those without sFGR and would prove useful to guide risk stratification and antenatal surveillance and tailored counselling to parents.

In our review, we did not find a significant difference in the risk of PE between DCDA twin pregnancies complicated by sFGR and those without sFGR. Caution should be exercised while interpreting this finding. Firstly, we were limited by the number of studies such that only two studies explored this outcome. Secondly, it is not clear whether these studies have employed singleton or twin-specific reference charts. The literature on the association between preeclampsia and FGR in DCDA twin pregnancies is conflicting and depends on the reference charts used for the diagnosis of FGR.[41-47] In studies where the diagnosis of FGR was based on singleton reference charts, there was no association between FGR and PE as many more twins were being classified as FGR.[41] However, in recent studies where investigators employed twin-specific charts, the association of PE with FGR in twin pregnancies was notable and significant.[44,46] Proctor et al have demonstrated that in twins, when using a twin-based reference to define FGR, hypertensive disorders of pregnancy in twin gestations were associated with a similar increase in the risk of FGR to that seen in singletons (11.8% vs 4.7%, adjusted relative risk, 2.37, 95% CI, 1.69-3.34).

We did not find any difference in the rates of PTB prior to 34 weeks in DCDA twin pregnancies affected by sFGR and those not complicated by sFGR. Similar to PE, we were limited in our analysis as only 2 studies were cross matched for this outcome. Most of the professional bodies recommend elective delivery of uncomplicated DCDA twin pregnancies at 37 weeks' gestation to reduce the risk of stillbirth.[16,48,49] Unfortunately, we could not comprehensively analyse for risk of PTB <32 and <28 weeks which we believe would have been more meaningful and clinically informative. Additionally, we could not analyse iatrogenic and spontaneous preterm birth separately, which is an important consideration as managing DCDA twin pregnancies with sFGR needs judicious decision-making to avoid the risk of inappropriate iatrogenic prematurity for the normally growing co-twin whilst aiming to avoid stillbirth of the smaller fetus.

Clinical and research implications

The management and outcomes of DCDA twin pregnancies with sFGR have not been extensively addressed in the published literature. The ISUOG twin guideline suggests that DCDA twin pregnancies with sFGR should be managed as growth restricted singleton pregnancies.[16] However, this management strategy is largely extrapolated from studies carried out exclusively in singleton pregnancies, ignoring the inherent differences between multiple and singleton pregnancies and the added complexity of, as well as the impact of iatrogenic prematurity on, the normally growing co-twin. Future studies are needed to establish whether a different surveillance and management approach in these pregnancies could improve their perinatal outcomes.

The additional information from this systematic review could help parents to understand the actual risk of adverse perinatal outcomes and to make decisions for their care that is best suited to them. This review also highlighted the lack of large-scale prospective studies with high-quality data that focus on DCDA twin pregnancies complicated by sFGR. In our review, we have identified definite gaps in our knowledge of the natural history of sFGR and the direction of future research should be focussed on the stratification of sFGR according to the gestational age of onset and the pattern of discordance over serial scans.

Conclusions

DCDA twin pregnancies complicated by sFGR are at higher risk of perinatal mortality and morbidity compared to those not affected. The pooled estimates of the perinatal mortality and morbidity, as well as a quantified excess risk when compared with twin pregnancies without sFGR, are pertinent in risk stratification, tailoring antenatal surveillance, and counseling the parents. The findings from this systematic review highlight the need for intensive fetal surveillance of twin pregnancies with sFGR to improve their perinatal outcomes. Further large prospective studies with shared protocols and uniform outcome reporting measures for prenatal management of DCDA pregnancies with sFGR are needed to compare the different management options and timing at delivery when sFGR is detected.

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REFERENCES:

1. Draper ES, Gallimore ID, Kurinczuk JJ, Kenyon S (Eds.) on behalf of MBRRACE-UK. MBRRACE-UK 2019 Perinatal Confidential Enquiry: Stillbirths and neonatal deaths in twin pregnancies. The Infant Mortality and Morbidity Studies, Department of Health Sciences, University of Leicester: Leicester, 2021.
2. Gestation-specific Infant Mortality in England and Wales - Office for National Statistics [Internet]. [cited 2023 Mar 18]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofdeath/datasets/gestationspecificinfantmortalityinenglandandwalesreferencetables
3. Buca D, Pagani G, Rizzo G, Familiari A, Flacco ME, Manzoli L, Liberati M, Fanfani F, Scambia G, D'Antonio F. Outcome in monochorionic twin pregnancies with selective intrauterine growth restriction according to the umbilical artery Doppler pattern of the smaller twin: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2017; **50**:559-568
4. Townsend R, D'Antonio F, Sileo FG, Kumbay H, Thilaganathan B, Khalil A. Perinatal outcome of monochorionic twin pregnancy complicated by selective fetal growth restriction according to management: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2019; **53**: 36-46.
5. D'Antonio F, Odibo A, Berghella V, Khalil A, Kack K, Saccone G, Prefumo F, Buca D, Liberati M, Pagani G, Acharya G. Systematic review and meta-analyses of monoamniotic twin pregnancies: Perinatal mortality, timing of delivery and prenatal management. *Ultrasound Obstet Gynecol* 2019; **53**:166-174.
6. Townsend R, Khalil A. Fetal growth restriction in twins. *Best Pract Res Clin Obstet Gynaecol* 2018; **49**: 79–88.
7. Cheong-See F, Schuit E, Arroyo-Manzano D, Khalil A, Barrett J, Joseph KS, Asztalos E, Hack K, Lewi L, Lim A, Liem S, Norman JE, 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 BW, Zamora J, Thilaganathan B, Thangaratinam S; Global Obstetrics Network (GONet) Collaboration. Prospective risk of stillbirth and neonatal complications in twin pregnancies: systematic review and meta-analysis. *BMJ* 2016; **354**: i4353.
8. D'Antonio F, Khalil A, Dias T, Thilaganathan B; Southwest Thames Obstetric Research Collaborative (STORK). Early fetal loss in monochorionic and dichorionic twin pregnancies: analysis of the Southwest Thames Obstetric Research Collaborative (STORK) multiple pregnancy cohort. *Ultrasound Obstet Gynecol* 2013; **41**: 632-6.

9. Coutinho Nunes F, Domingues AP, Vide Tavares M, Belo A, Ferreira C, Fonseca E, Moura P. Monochorionic versus dichorionic twins: Are obstetric outcomes always different? *J Obstet Gynaecol* 2016; **36**: 598-601.
10. Khalil A, Beune I, Hecher K, Wynia K, Ganzevoort W, Reed K, Lewi L, Oepkes D, Gratacos E, Thilaganathan B, Gordijn SJ. Consensus definition and essential reporting parameters of selective fetal growth restriction in twin pregnancy: a Delphi procedure. *Ultrasound Obstet Gynecol* 2019; **53**: 47-54.
11. Koch AK, Burger RJ, Schuit E, Mateus JF, Goya M, Carreras E, Biancolin SE, Barzilay E, Soliman N, Cooper S, Metcalfe A, Lodha A, Fichera A, Stagnati V, Kawamura H, Rustico M, Lanna M, Munim S, Russo FM, Nassar A, Rode L, Lim A, Liem S, Grantz KL, Hack K, Combs CA, Serra V, Perales A, Khalil A, Liu B, Barrett J, Ganzevoort W, Gordijn SJ, Morris RK, Mol BW, Li W. Timing of Delivery for Twins With Growth Discordance and Growth Restriction: An Individual Participant Data Meta-analysis. *Obstet Gynecol* 2022;**139**: 1155-1167.
12. Saccone G, Khalil A, Thilaganathan B, Glinianaia SV, Berghella V, D'Antonio F, MONOMONO, NorSTAMP and STORK research collaboratives. Weight discordance and perinatal mortality in monoamniotic twin pregnancy: analysis of MONOMONO, NorSTAMP and STORK multiple-pregnancy cohorts. *Ultrasound Obstet Gynecol* 2020; **55**: 332-338.
13. D'Antonio F, Odibo A, Prefumo F, Khalil A, Buca D, Flacco M, Liberati M, Manzoli L, Acharya G. Weight discordance and perinatal mortality in twin pregnancies: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2018; **52**:11-23.
14. Di Mascio D, Acharya G, Khalil A, Odibo A, Prefumo F, Liberati M, Buca D, Manzoli L, Flacco ME, Brunelli R, Benedetti Panici P, D'Antonio F. Birthweight discordance and neonatal morbidity in twin pregnancies: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand* 2019; **98**: 1245-1257.
15. Khalil AA, Khan N, Bowe S, Familiari A, Papageorghiou A, Bhide A, Thilaganathan B. Discordance in fetal biometry and Doppler are independent predictors of the risk of perinatal loss in twin pregnancies. *Am J Obstet Gynecol* 2015; **213**: 222.e1-222.e10.
16. Khalil A, Rodgers M, Baschat A, Bhide A, Gratacos E, Hecher K, Kilby MD, Lewi L, Nicolaides KH, Oepkes D, Raine-Fenning N, Reed K, Salomon LJ, Sotiriadis A, Thilaganathan B, Ville Y. ISUOG Practice Guidelines: role of ultrasound in twin pregnancy. *Ultrasound Obstet Gynecol* 2016; **47**: 247-63.
17. Gratacós E, Lewi L, Muñoz B, Acosta-Rojas R, Hernandez-Andrade E, Martinez JM, Carreras E, Deprest J. A classification system for selective intrauterine growth restriction in monochorionic pregnancies according to umbilical artery Doppler flow in the smaller twin. *Ultrasound Obstet Gynecol* 2007; **30**: 28-34.

18. Denbow ML, Cox P, Taylor M, Hammal DM, Fisk NM. Placental angioarchitecture in monochorionic twin pregnancies: relationship to fetal growth, fetofetal transfusion syndrome, and pregnancy outcome. *Am J Obstet Gynecol* 2000; **182**: 417–426.
19. Vanlieferinghen S, Anselem O, Le Ray C, Shen Y, Marcellin L, Goffinet F. Prognostic value of umbilical and cerebral Doppler in fetal growth restriction: comparison of dichorionic twins and singletons. *PLoS One* 2015; **10**: e0123067.
20. Hiersch L, Okby R, Freeman H, Rosen H, Nevo O, Barrett J, Melamed N. Differences in fetal growth patterns between twins and singletons. *J Matern Fetal Neonatal Med* 2020; **33**: 2546-2555.
21. Henderson LK, Craig JC, Willis NS, Tovey D, Webster AC. How to write a Cochrane systematic review. *Nephrology (Carlton)* 2010; **15**: 617-624.
22. 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.
23. Newcastle-Ottawa Scale for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
24. Higgins J, Thompson S, Deeks J, Altman D. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. *J Health Serv Res Policy* 2002; **7**: 51–61.
25. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test BMJ. 1997; **315**: 629–634.
26. Hunter JP, Saratzis A, Sutton AJ, Boucher RH, Sayers RD, Bown MJ. In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. J Clin Epidemiol 2014 Aug; 67: 897–903.
27. Hoong MF, Chao AS, Chang SD, Lien R, Chang YL. Association between respiratory distress syndrome of newborns and fetal growth restriction evaluated using a dichorionic twin pregnancy model. *J Gynecol Obstet Hum Reprod* 2022; **51**: 102383.
28. Lyu S, Gao L, Sun J, Zhao X, Wu Y, Hua R, Wang Y. The association between maternal complications and small for gestational age in twin pregnancies using singleton and twin birth weight references. *J Matern Fetal Neonatal Med* 2022; **35**: 7459-7465.
29. Antonakopoulos N, Pateisky P, Liu B, Kalafat E, Thilaganathan B, Khalil A. Selective Fetal Growth Restriction in Dichorionic Twin Pregnancies: Diagnosis, Natural History, and Perinatal Outcome. *J Clin Med* 2020; **9**: 1404.
30. Ražem K, Bombač L, Tul N, Blickstein I. Neonatal morbidity and mortality among growth-discordant dichorionic twins, classified according to birth weight of the smaller twin: a population-based cohort study. *J Matern Fetal Neonatal Med* 2020; **33**: 2608–2611.

31. Yang CY, Hoong MF, Li CS, Li WF, You SH, Lee YC, Peng HH, Chueh HY, Chao AS, Cheng PJ, Chang SD, Lien R, Chang YL. Association between intrauterine growth restriction and patent ductus arteriosus: Use of a dichorionic twin pregnancy model. *Taiwan J Obstet Gynecol* 2021; 60: 517-522.
32. Barber E, Weiner E, Feldstein O, Dekalo A, Mizrachi Y, Gonullu DC, Bar J, Schreiber L, Kovo M. The differences in placental pathology and neonatal outcome in singleton vs. twin gestation complicated by small for gestational age. *Arch Gynecol Obstet* 2018; **298**: 1107-1114.
33. Algeri P, Frigerio M, Lamanna M, Petrova PV, Cozzolino S, Incerti M, Mastrolia SA, Roncaglia N, Vergani P. Selective IUGR in dichorionic twins: what can Doppler assessment and growth discordancy say about neonatal outcomes? *J Perinat Med* 2018; **46**: 1028-1034.
34. Biron-Shental T, Many A, Wiser A, Shechter-Maor G, Sukenik-Halevy R, Berkovitz A. Fertility treatment and dichorionic discordant twins - are they related? *J Perinat Med* 2016; **44**: 857–861.
35. D'Antonio F, Khalil A, Dias T, Thilaganathan B, Southwest Thames Obstetric Research Collaborative (STORK). Weight discordance and perinatal mortality in twins: analysis of the Southwest Thames Obstetric Research Collaborative (STORK) multiple pregnancy cohort. *Ultrasound Obstet Gynecol* 2013; **41**: 643-648.
36. Suzuki S, Inde Y, Hiraizumi Y, Miyake H. Growth Discordance is not an Independent Risk Factor for Adverse Perinatal Outcomes in Twin Pregnancies. *J Clin Gynecol Obstet* 2012; **1**: 31–35.
37. Mahony R, Mulcahy C, Mcauliffe F, Herlihy CO, Carroll S, Foley ME. Fetal death in twins. *Acta Obstet Gynecol Scand* 2011; **90**: 1274-1280.
38. Acosta-Rojas R, Becker J, Munoz-Abellana B, Ruiz C, Carreras E, Gratacos E; Catalunya and Balears Monochorionic Network. Twin chorionicity and the risk of adverse perinatal outcome. *Int J Gynaecol Obstet* 2007; 96: 98-102.
39. Adegbite AL, Castille S, Ward S, Bajoria R. Prevalence of cranial scan abnormalities in preterm twins in relation to chorionicity and discordant birth weight. *Eur J Obstet Gynecol Reprod Biol* 2005; **119**: 47–55.
40. Multifetal Gestations: Twin, Triplet, and Higher-Order Multifetal Pregnancies: ACOG Practice Bulletin, Number 231. *Obstetrics & Gynecology* 2021; **137**: e145.
41. Fox NS, Saltzman DH, Oppal S, Klauser CK, Gupta S, Rebarber A. The relationship between preeclampsia and intrauterine growth restriction in twin pregnancies. *Am J Obstet Gynecol* 2014; **211**: 422.e1-5.

42. Wu D, Huang L, He Z, Huang X, Fang Q, Luo Y. Preeclampsia in twin pregnancies: association with selective intrauterine growth restriction. *J Matern Fetal Neonatal Med* 2016; **29**:1967–1971.
43. Qiao P, Zhao Y, Jiang X, Xu C, Yang Y, Bao Y, Xie H, Ying H. Impact of growth discordance in twins on preeclampsia based on chorionicity. *Am J Obstet Gynecol* 2020; **223**: 572.e1-572.e8.
44. Proctor LK, Kfouri J, Hiersch L, Aviram A, Zaltz A, Kingdom J, Barrett J, Melamed N. Association between hypertensive disorders and fetal growth restriction in twin compared with singleton gestations. *Am J Obstet Gynecol* 2019; **221:** 251.e1-251.e8.
45. Hiersch L, Barrett J, Fox NS, Rebarber A, Kingdom J, Melamed N. Should twin-specific growth charts be used to assess fetal growth in twin pregnancies? *Am J Obstet Gynecol* 2022; **227**: 10–28.
46. Giorgione V, Bhide A, Bhate R, Reed K, Khalil A. Are Twin Pregnancies Complicated by Weight Discordance or Fetal Growth Restriction at Higher Risk of Preeclampsia? *Journal of Clinical Medicine* 2020; **9**: 3276.
47. Erez O, Vardi IS, Hallak M, Hershkovitz R, Dukler D, Mazor M. Preeclampsia in twin gestations: association with IVF treatments, parity and maternal age. *J Matern Fetal Neonatal Med* 2006; **19**: 141–146.
48. Overview | Twin and triplet pregnancy | Guidance | NICE [Internet]. NICE; 2019 [cited 2023 Feb 17]. Available from: https://www.nice.org.uk/guidance/ng137
49. Mei-Dan E, Jain V, Melamed N, Lim KI, Aviram A, Ryan G, Barrett J. Guideline No. 428: Management of Dichorionic Twin Pregnancies. *J Obstet Gynaecol Can* 2022; **44**: 819-834.e1.

Figure legends

Figure 1 Systematic review flowchart

Figure 2 Pooled odd ratios (OR) and their 95% confidence intervals (CI) for the risk of intrauterine demise in dichorionic diamniotic (DCDA) twin pregnancies complicated compared to those not complicated by selective fetal growth restriction (sFGR)

Figure 3 Pooled odd ratios (OR) and their 95% confidence intervals (CI) for the risk of overall composite morbidity or admission to neonatal intensive care unit in dichorionic diamniotic (DCDA) twin pregnancies complicated compared to those not complicated by selective fetal growth restriction (sFGR)

Supporting information on the internet

Table S1 Search strategies

Table S2 Excluded studies and reason for the exclusion

Table 1. General characteristics of the included studies

Author	Year	Country	Study design	Period considered	GA at diagnosis	Stratification according to GA at birth or Doppler status	Definition adopted	Pregnancies	sFGR (n)
Hoong[27]	2022	Taiwan	Retrospective case-control	2012-2018	NR	Not performed	BW< 10th percentile and BW discordance (BWD) of ≥25%.	733	53
Lyu[28]	2021	China	Retrospective case-control	2013	NR	Not performed	BW < 10th centile	2005	110
Antonakopoulos[29]	2020	United Kingdom	Retrospective cohort	2000-2019	27 (22-28)	Performed	Delphi	1053	123
Razem[30]	2020	Slovenia	Retrospective cohort	2002-2016	≥22 weeks	Not performed	BW discordance of >25% and a twin with BW <10th centile	270	270
Yang[31]	2020	Taiwan	Retrospective cohort	2013-2018	NR	Not performed	BW discordance of >25% and a twin with BW <10th centile	53	53
Barber[32]	2018	Israel	Retrospective cohort	2008-2017	≥24 weeks	Not performed	BW ≤ 10th percentile in one twin	66	66

Algeri[33]	2017	Italy	Retrospective cohort	2008-2015	≥24 weeks	Performed	AC <10th centile in one twin, and AC >10 in the other twin	59	59
Biron-Shental[34]	2015	Israel	Retrospective case-control	Not reported	≥24 weeks	Not performed	difference of at least 20% and BW <10th centile in one twin	510	47
D'Antonio[35]	2013	United Kingdom	Retrospective case-control	2000-2010	≥24 weeks	Not performed	Delphi	2476	247
Suzuki[36]	2012	Japan	Retrospective case-control	2002-2010	≥22 weeks	Not performed	BW discordance of >20%BW or EFW <10th centile of one twin	609	234
Mahony[37]	2011	Ireland	Retrospective cohort	1997-2006	≥23 weeks + 6 days	Not performed	BW < 5th centile	818	159
Acosta-rojas[38]	2007	Spain	Prospective case-control	NR	NR	Not performed	One twin with EFW) < 10th or 5th percentile	106	5
Adgebite[39]	2004	United Kingdom	Retrospective case-control	1991-19997	NR	Not performed	BW discordance of >20% and a twin with AC <10th centile and abnormal Doppler	75	20

GA, gestational age; NR, not reported; EFW, estimated fetal weight; AC, abdominal circumference

Table 2. Quality assessment of the included studies according to the Newcastle-Ottawa Scale (NOS) for cohort studies; a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Author	Year	Selection	Comparability	Outcome
Hoong[27]	2022	**	**	**
Lyu[28]	2021	***	**	**
Antonakopoulos[29]	2020	***	**	**
Razem[30]	2020	**	**	**
Yang[31]	2020	**	*	**
Barber[32]	2018	***	**	**
Algeri[33]	2017	**	**	*
Biron-Shental[34]	2015	**	**	**
D'Antonio[35]	2013	***	**	**
Suzuki[36]	2012	**	**	**
Mahony[37]	2011	**	**	*
Acosta-rojas[38]	2007	**	**	**
Adgebite[39]	2004	***	*	**

Only first author is given for each study.

Study can be awarded maximum of one star for each numbered item within selection and outcome categories.

Maximum of two stars can be given for comparability.

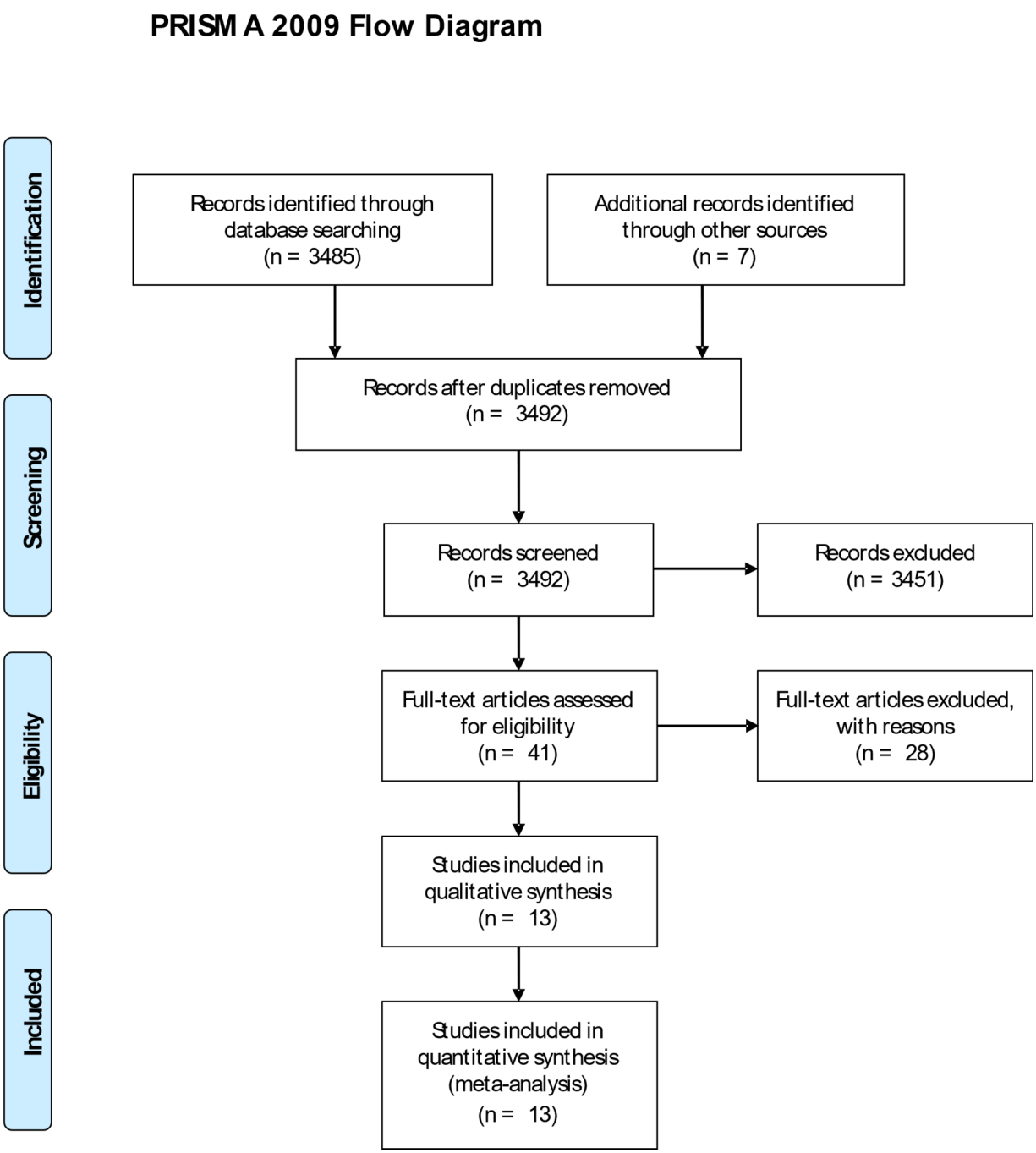
Table 3: Pooled proportions (95% CI) for the different outcomes explored in the present systematic review in dichorionic diamniotic (DCDA) twin pregnancies complicated by selective fetal growth restriction (sFGR)

Outcome	Studies (n)	Cases (n/N)	Pooled proportions (95% CI)	I^2 (%)		Studies (n)	Cases (n/N)	Pooled proportions (95% CI)	I^2 (%)
DCDA pregnancies complicated by sFGR						***DCDA pregnancies not complicated by sFGR***			
Intra-uterine death	6	63/1912	2.56 (1.07-4.65)	80.1		4	31/6728	0.58 (0.29-9.73)	55.4
Neonatal death	7	18/1404	1.52 ((0.83-2.41)	18.8		3	26/4770	2.17 (0.13-6.57)	91.1
Perinatal death	4	62/1126	5.21 (3.49-7.26)	34.7		2	36/4660	1.74 (0.05-5.71)	89.7
At least one twin alive	4	252/293	99.83 (99.03-99.98)	0		2	2302/2330	99.45 (97.74-99.76)	36.5
Both twins alive	4	225/293	92.30 (85.04-97.29)	43.4		2	2300/2330	98.67 (98.17-99.10)	0
Preterm birth < 37 weeks	5	467/628	84.11 (55.64-99.17)	98		3	1875/3010	69.06 (45.41-88.35)	99.1
Preterm birth < 34 weeks	3	94/522	18.35 (4.42-38.92)	95.9		2	356/2604	10.15 (3.09-20.65)	96.6
Preterm birth < 32 weeks	4	76/563	13.04 (9.46-17.09)	29.7		2	182/2330	7.84 (6.79-8.97)	0
Preterm birth < 28 weeks	3	6/486	1.47 (0.59-2.27)	0		2	47/2604	1.84 (1.26-2.2.39)	0
Pre-eclampsia	5	99/516	19.87 (12.41-28.58)	79.4		3	401/2950	12.82 (10.43-15.41)	69.3
Composite morbidity	6	402/1546	28.23 (7.81-55.13)	99.1		3	540/3405	13.87 (6.50-23.46)	97.7

Apgar score < 7 at 5 minutes	3	18/1105	1.06 (0.03-3.52)	86.3		1	2/134	-	-
Neurologic morbidity	-	-	-	-		-	-	-	-
Respiratory morbidity	4	87/759	18.29 (3.25-41.73)	97		2	151/1555	9.88 (8.11-11.80)	14.4
Infectious morbidity	-	-	-	-		-	-	-	-
Necrotizing enterocolitis	2	2/142	3.88 (0.27-18.84)	64.4		-	-	-	-
Retinopathy of prematurity	-	-	-	-		-	-	-	-
Admission to NICU	5	378/978	39.74 (17.42-64.59)	98		2	411/2045	16.29 (8.04-26.74)	-

Table 4: Pooled odd ratios (95% CI) for the different outcomes explored in the present systematic review in dichorionic twin pregnancies complicated compared to those non complicated by selective fetal growth restriction.

Outcome	Studies (n)	Cases (n/N)	Pooled proportions (95% CI)	I^2 (%)	p-value
Intrauterine demise	4	30/1290 vs 31/6728	5.23 (3.18-8.58)	81.8	<0.001
Preterm birth <34 weeks of gestation	2	84/481 vs 356/2604	1.61 (0.75-3.46)	76.3	0.220
Pre-eclampsia	2	37/287 vs 125/1055	1.21 (0.78-1.87)	28	0.465
Composite morbidity or admission to neonatal unit	3	156/360 vs 540/3045	3.22 (1.85-5.60)	76.2	0.012



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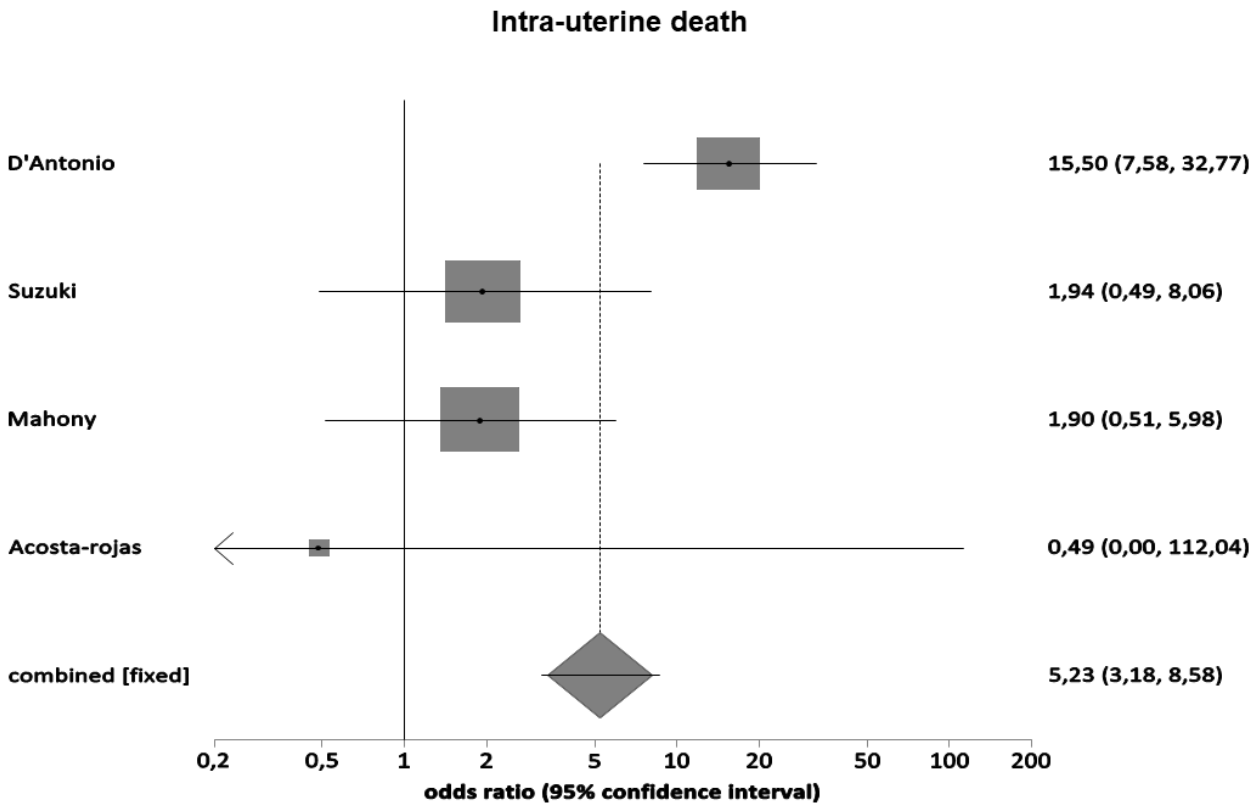

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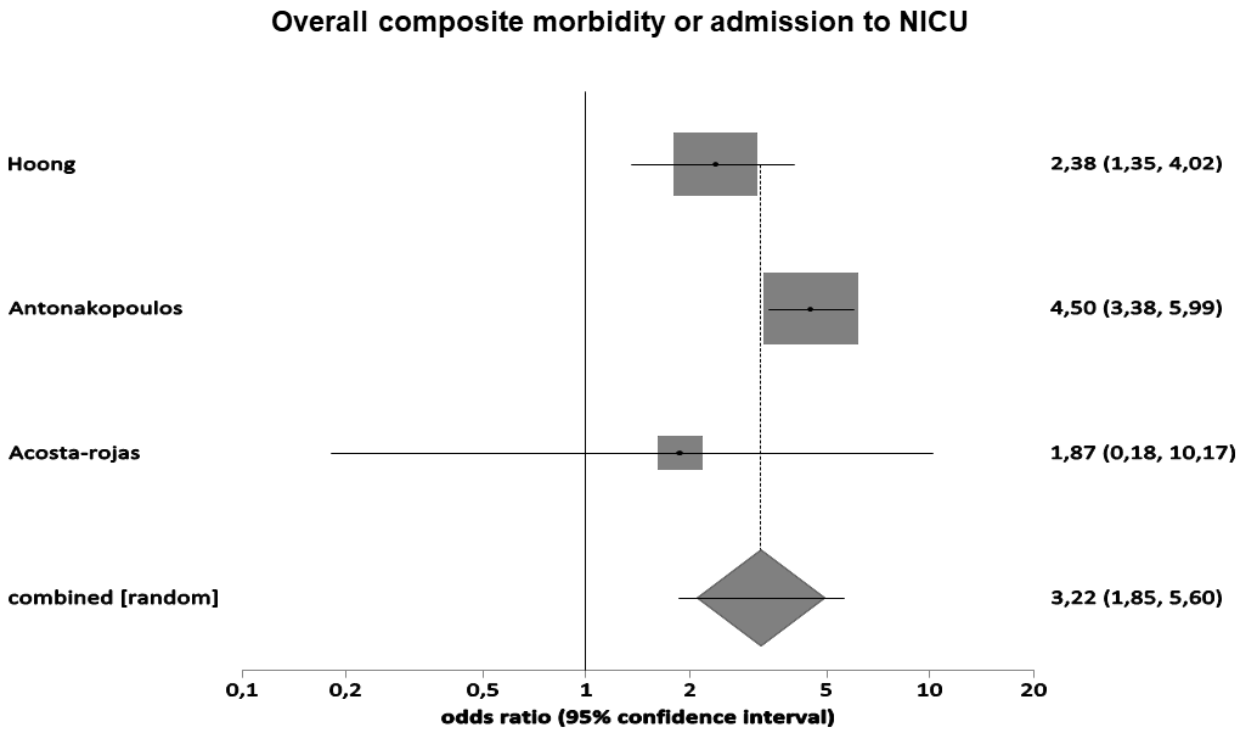

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