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

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KEYWORDS: fetal growth restriction; intrauterine demise; morbidity; mortality; neonatal death; outcome; size discordance; small-for-gestational age; stillbirth; twin pregnancies

CONTRIBUTION

What are the novel findings of this work?
When compared with uncomplicated dichorionic diamniotic (DCDA) twin pregnancies, DCDA twin pregnancies with selective fetal growth restriction (sFGR) have 5-fold higher odds of intrauterine death and 3-fold higher odds of composite neonatal morbidity or admission to the neonatal intensive care unit. This study presents estimates of the risk of adverse outcomes in these complicated pregnancies.

What are the clinical implications of this work?
DCDA twin pregnancies with sFGR are at high risk of perinatal morbidity and mortality. The findings should facilitate counseling and management of complicated DCDA twin pregnancies, in particular those affected by sFGR. Twin-specific, rather than singleton, outcome data should be used.

ABSTRACT

Objective *Most of the published literature on selective fetal growth restriction (sFGR) has focused on monochorionic twin pregnancies. The aim of this systematic review was to report on the outcome of dichorionic diamniotic (DCDA) twin pregnancies complicated by sFGR.*

Methods *MEDLINE, EMBASE and The Cochrane Library databases were searched. The inclusion criteria were DCDA twin pregnancies complicated by sFGR. The outcomes explored were intrauterine death (IUD), neonatal death and perinatal death (PND), survival of at least one and both twins, preterm birth (PTB) (either spontaneous or iatrogenic) prior to 37, 34, 32 and 28 weeks' gestation, pre-eclampsia (PE) or gestational hypertension, neurological, respiratory and infectious morbidity, Apgar score < 7 at 5 min, necrotizing enterocolitis, retinopathy of prematurity and admission to the neonatal intensive care unit (NICU). A composite outcome of neonatal morbidity, defined as the occurrence of respiratory, neurological or infectious morbidity, was also evaluated. Random-effects meta-analysis was used to analyze the data, and results are reported as pooled proportion or odds ratio with 95% CI.*

Results *Thirteen studies reporting on 1339 pregnancies with sFGR and 6316 pregnancies without sFGR were included. IUD occurred in 2.6% (95% CI, 1.1–4.7%) of fetuses from DCDA pregnancies with sFGR and 0.6% (95% CI, 0.3–9.7%) of those from DCDA pregnancies without sFGR, while the respective values for PND were 5.2% (95% CI, 3.5–7.3%) and 1.7% (95% CI, 0.1–5.7%). Spontaneous or iatrogenic PTB before 37 weeks complicated 84.1% (95% CI, 55.6–99.2%) of pregnancies with sFGR and 69.1% (95% CI, 45.4–88.4%) of those without sFGR. The respective values for PTB before 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 with sFGR and 10.2% (95% CI, 3.1–20.7%), 7.8% (95% CI,*

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6.8–9.0%) and 1.8% (95% CI, 1.3–2.4%) in those without sFGR. PE or gestational hypertension complicated 19.9% (95% CI, 12.4–28.6%) of pregnancies with sFGR and 12.8% (95% CI, 10.4–15.4%) of those without sFGR. Composite morbidity occurred in 28.2% (95% CI, 7.8–55.1%) of fetuses from pregnancies with sFGR and 13.9% (95% CI, 6.5–23.5%) of those from pregnancies without sFGR. When stratified according to the sFGR status within a twin pair, composite morbidity occurred in 39.0% (95% CI, 11.1–71.5%) of growth-restricted fetuses and 29.9% (95% CI, 3.5–65.0%) of appropriately grown fetuses (odds ratio (OR), 1.9 (95% CI, 1.7–3.1)), while the respective values for PND were 3.0% (95% CI, 1.8–4.5%) and 1.6% (95% CI, 0.9–2.6%) (OR, 2.1 (95% CI, 1.0–4.1)). On risk analysis, DCDA pregnancies complicated by sFGR had a significantly higher risk of IUD (OR, 5.2 (95% CI, 3.2–8.6)) and composite morbidity or admission to the NICU (OR, 3.2 (95% CI, 1.9–5.6)) compared to those without sFGR, while there was no difference in the risk of PTB before 34 weeks (P = 0.220) or PE/gestational hypertension (P = 0.210).

***Conclusions** DCDA twin pregnancies complicated by sFGR are at high risk of perinatal morbidity and mortality. The findings of this systematic review are relevant for counseling and management of complicated DCDA twin pregnancies, in which twin-specific, rather than singleton, outcome data should be used.* © *2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Twin pregnancies are at an increased risk of perinatal morbidity and mortality, primarily owing to preterm birth (PTB) and fetal growth restriction (FGR)[1–9]. According to the recent Delphi consensus, selective FGR (sFGR) in dichorionic 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 ≥ 25% and umbilical artery (UA) pulsatility index of the smaller twin > 95th centile)[10].

Growth restriction in twin pregnancies has been established as an independent predictor of adverse perinatal outcome[11–15]. In monochorionic twin pregnancies, sFGR is stratified further according to the hemodynamic pattern of the end-diastolic flow in the UA of the smaller fetus into Types I, II and III, with sFGR Types II and III exhibiting a higher risk of perinatal morbidity and mortality[16–18]. Conversely, there is less evidence regarding the risk and perinatal outcome associated with sFGR in dichorionic twin pregnancies. In monochorionic twin pregnancies, sFGR is attributed to unequal sharing of the single placenta, while, in dichorionic twin pregnancies with sFGR, the most likely etiology is deemed to be uteroplacental insufficiency[6].

Guidelines on the management of dichorionic twin pregnancies complicated by sFGR recommend management in line with that of growth-restricted singletons[16]. However, the prognostic value of abnormal fetal Doppler ultrasound may not have the same significance for growth-restricted twins as it does for growth-restricted singletons, which should be considered when a decision for early delivery is made[19,20].

The literature on the natural history of dichorionic twin pregnancies is limited by variable diagnostic criteria for sFGR, small sample size of the published studies, heterogeneity in outcome assessment and reporting and heterogeneity in gestational age (GA) at diagnosis. The severity of adverse perinatal outcomes in dichorionic twin pregnancies is perceived to be lower than that in monochorionic twin pregnancies. However, management of dichorionic twin pregnancies complicated by sFGR remains challenging. The aim of this systematic review and meta-analysis of the available literature was to evaluate pregnancy and perinatal outcomes of dichorionic diamniotic (DCDA) twin pregnancies complicated by sFGR.

METHODS

Protocol, information sources and literature search

This review was performed according to an *a-priori* designed protocol recommended for systematic reviews and meta-analyses[21,22]. MEDLINE, EMBASE and The Cochrane Library databases were searched electronically on 28 April 2022, followed by an update on 17 August 2022, utilizing a combination of relevant medical subject heading (MeSH) terms, keywords and word variants for 'growth restriction', 'twin pregnancies', 'ultrasound' and 'outcome' (Table S1). The search and selection criteria were restricted to the English language. Reference lists of relevant articles and reviews were searched manually for additional reports. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines were followed. The study was registered with the PROSPERO database (registration number: CRD42022361648).

Outcome measures, study selection and data collection

The inclusion criteria were DCDA twin pregnancies complicated by sFGR, defined according to the Delphi consensus[10] as the presence of 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 UA pulsatility index of the smaller twin > 95th centile) or as EFW, birth weight (BW) or abdominal circumference < 10th percentile with EFW or BW discordance of > 20% or 25% in studies published before the consensus paper.

The outcomes explored were as follows: intrauterine death (IUD), defined as fetal loss after 20 weeks' gestation; neonatal death (NND), defined as death until 28 days after birth; perinatal death (PND), defined as the sum

of IUD and NND; survival of at least one twin; survival of both twins; PTB (spontaneous or iatrogenic) prior to 37, 34, 32 and 28 weeks; pre-eclampsia (PE), defined as new-onset hypertension and proteinuria **or** new-onset hypertension and significant end-organ dysfunction with or without proteinuria after 20 weeks or postpartum in a previously normotensive patient, or gestational hypertension, defined as new-onset hypertension without proteinuria; neurological morbidity, defined as occurrence of intraventricular hemorrhage (Grade III and IV) or periventricular leukomalacia (Grade II); respiratory morbidity, defined as occurrence of respiratory distress syndrome or need for mechanical ventilation; infectious morbidity, defined as occurrence of neonatal sepsis; Apgar score < 7 at 5 min; necrotizing enterocolitis, defined as ischemic necrosis of the intestinal mucosa; retinopathy of prematurity, defined as a developmental vascular proliferative disorder that occurs in the retina with incomplete retinal vascularization; and admission to the neonatal intensive care unit (NICU). Furthermore, we evaluated a composite outcome of neonatal morbidity, defined as the occurrence of respiratory, neurological or infectious morbidity.

All outcomes were explored in the overall population of twin pregnancies complicated by, and in those not complicated by, sFGR. Furthermore, we planned subgroup analyses according to GA at diagnosis and Doppler status. PND was analyzed only in studies reporting both IUD and NND.

Only studies reporting on the outcome of DCDA twin pregnancies complicated by sFGR were considered suitable for inclusion in this review. Studies reporting on the incidence of the explored outcomes in DCDA twin pregnancies with EFW or BW discordance without stating that the pregnancy was affected by sFGR were excluded. Studies including sFGR cases from monochorionic diamniotic or monoamniotic twin pregnancies or pregnancies with structural or chromosomal anomalies and studies 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 made them less relevant. Only full-text articles were considered eligible for inclusion. Case reports, conference abstracts and case series with fewer than five cases were excluded to avoid publication bias.

Two authors (S.P., L.M.) 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 relevant papers were obtained, and two reviewers (S.P., F.D.A.) independently extracted relevant data regarding study characteristics and pregnancy outcomes. Inconsistencies were resolved through discussion among the reviewers until a consensus was reached or through discussion with a third author (A.K.). If more than one study had been 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 and risk of bias

Quality assessment of the included studies was performed using the Newcastle–Ottawa scale (NOS) for case–control and cohort studies. According to the NOS, each study is judged on three broad perspectives, including selection of study groups, comparability of study groups and ascertainment of the outcome of interest. Assessment of the selection domain includes evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and demonstration that the outcome of interest was not present at the start of the study. Assessment of the comparability domain includes evaluation of the comparability of cohorts based on design or analysis. Finally, ascertainment of the outcome of interest includes evaluation of the type of assessment of the outcome of interest and length and adequacy of follow-up. According to the NOS, a study can be awarded a maximum of one star for each numbered item within the selection and outcome categories[23], and a maximum of two stars can be given for comparability.

Statistical analysis

First, we planned to report on the incidence of each explored outcome in DCDA twin pregnancies complicated by, and those not complicated by, sFGR. We used random-effects meta-analysis to combine data, and results are reported as pooled proportions with 95% 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 was used as the denominator for the assessment of PTB, PE and the presence of at least one and two survivors. Second, we aimed to compare the risk of each explored outcome in DCDA pregnancies complicated, *vs* those not complicated, by sFGR, including only studies in which pregnancies with sFGR were compared with a matched population of those without sFGR. However, a comprehensive pooled risk assessment was not possible for all the explored outcomes because of the small number of included studies per each analysis and the even smaller number of events. Therefore, we performed meta-analyses comparing the risk of select outcomes between pregnancies complicated by *vs* those not complicated by sFGR. Finally, we aimed to report on the risk of morbidity and mortality in the larger *vs* the smaller twin. For the purpose of these analyses, we used random-effects meta-analysis, reporting the results as odds ratios (ORs) with 95% CIs.

Between-study heterogeneity was explored using the I^2 statistic, which represents the proportion 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 $\geq 50\%$ indicate a substantial level of heterogeneity[24]. All analyses

were performed using StatsDirect Statistical Software (StatsDirect Ltd, Cambridge, UK).

Funnel plots displaying the outcome rate from individual studies *vs* their precision (1/standard error) were used with an exploratory aim[25]. The test for funnel plot asymmetry was not used when the total number of publications included for each outcome was less than 10 because, in that case, the power of the test would have been too low to distinguish chance from real asymmetry[26].

RESULTS

Study selection and characteristics

The literature search identified 3485 records, with an additional seven 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 systematic review and meta-analysis (Tables 1 and S2, Figure 1). These 13 studies included 1339 cases complicated by sFGR and 6316 cases uncomplicated by sFGR following removal of overlapping cases. The results of the quality assessment of the included studies using the NOS tool are presented in Table 2. The included studies showed an overall good score regarding selection and comparability of the study groups, as well as ascertainment of the outcome of interest. The major limitations of most studies included retrospective design, heterogeneity in the outcomes observed and lack of stratification of the analysis according to GA at diagnosis and Doppler status for most of the included studies.

Synthesis of results

IUD occurred in 2.6% (95% CI, 1.1–4.7%) of fetuses from DCDA twin pregnancies with sFGR and 0.6% (95% CI, 0.3–9.7%) of those from DCDA twin pregnancies without sFGR, while the respective values for NND were 1.5% (95% CI, 0.8–2.4%) and 2.2% (95% CI,

Table 1 Characteristics of studies included in systematic review and meta-analysis

Study	*Country*	*Study design*	*Study period*	*GA at diagnosis (weeks)*	*Stratification according to GA at birth or Doppler status*	*sFGR definition adopted*	*Pregnancies (n)*	*sFGR (n)*
Hoong (2022)[27]	Taiwan	Retro case–control	2012–2018	NR	Not performed	BW < 10th centile and BW discordance ≥ 25%	733	53
Lyu (2022)[28]	China	Retro case–control	2013	NR	Not performed	BW < 10th centile	2005	110
Yang (2021)[31]	Taiwan	Retro cohort	2013–2018	NR	Not performed	BW discordance > 25% and BW < 10th centile in one twin	53	53
Antonakopoulos (2020)[29]*	UK	Retro cohort	2000–2019	27 (22–28)	Performed	Delphi	1053	123
Ražem (2020)[30]	Slovenia	Retro cohort	2002–2016	≥ 22	Not performed	BW discordance > 25% and BW < 10th centile in one twin	270	270
Algeri (2018)[33]	Italy	Retro cohort	2008–2015	≥ 24	Performed	AC < 10th centile in one twin and > 10th centile in other twin	59	59
Barber (2018)[32]	Israel	Retro cohort	2008–2017	≥ 24	Not performed	BW ≤ 10th centile in one twin	66	66
Biron-Shental (2016)[34]	Israel	Retro case–control	NR	≥ 24	Not performed	BW discordance ≥ 20% and BW < 10th centile in one twin	510	47
D'Antonio (2013)[35]*	UK	Retro case–control	2000–2010	≥ 24	Not performed	Delphi	2476	247
Suzuki (2012)[36]	Japan	Retro case–control	2002–2010	≥ 22	Not performed	BW discordance > 20% and BW or EFW < 10th centile in one twin	609	234
Mahony (2011)[37]	Ireland	Retro cohort	1997–2006	≥ 23 + 6	Not performed	BW < 5th centile	818	159
Acosta-Rojas (2007)[38]	Spain	Prosp case–control	NR	NR	Not performed	EFW < 10th or 5th centile in one twin	106	5
Adegbite (2005)[39]	UK	Retro case–control	1991–19 997	NR	Not performed	BW discordance > 20% and AC < 10th centile and abnormal Doppler in one twin	75	20

Only first author is given for each study.*Studies had partially overlapping cases, which were included only once in systematic review. AC, abdominal circumference; BW, birth weight; EFW, estimated fetal weight; GA, gestational age; NR, not reported; Prosp, prospective; Retro, retrospective; sFGR, selective fetal growth restriction.

0.1–6.6%) (Table 3). PND occurred in 5.2% (95% CI, 3.5–7.3%) of fetuses from pregnancies with sFGR and 1.7% (95% CI, 0.1–5.7%) of those from pregnancies without sFGR. Among DCDA pregnancies with sFGR, PND occurred in 3.0% (95% CI, 1.8–4.5%) of growth-restricted fetuses and 1.6% (95% CI, 0.9–2.6%) of appropriately grown twins. Survival of at least one twin was observed in 99.8% (95% CI, 99.0–100%) of pregnancies with sFGR and 99.5% (95% CI, 97.7–99.8%) of those without sFGR, while the respective values for survival of both twins were 92.3% (95% CI, 85.0–97.3%) and 98.7% (95% CI, 98.2–99.1%).

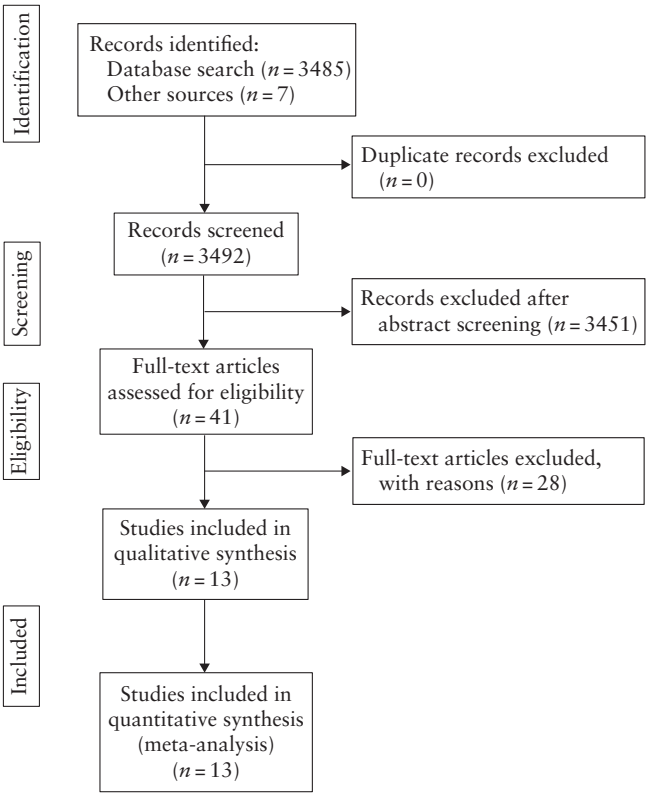

Figure 1 Flowchart summarizing inclusion of studies in systematic review and meta-analysis.

Table 2 Quality assessment of included studies according to Newcastle–Ottawa scale for cohort studies

Study	*Selection*	*Comparability*	*Outcome*
Hoong (2022)[27]	**	**	**
Lyu (2022)[28]	***	**	**
Yang (2021)[31]	**	*	**
Antonakopoulos (2020)[29]	***	**	**
Ražem (2020)[30]	**	**	**
Algeri (2018)[33]	**	**	*
Barber (2018)[32]	***	**	**
Biron-Shental (2016)[34]	**	**	**
D'Antonio (2013)[35]	***	**	**
Suzuki (2012)[36]	**	**	**
Mahony (2011)[37]	**	**	*
Acosta-Rojas (2007)[38]	**	**	**
Adegbite (2005)[39]	***	*	**

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.

Spontaneous or iatrogenic PTB before 37 weeks complicated 84.1% (95% CI, 55.6–99.2%) of pregnancies with sFGR and 69.1% (95% CI, 45.4–88.4%) of those without sFGR. The respective values for PTB before 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 with sFGR and 10.2% (95% CI, 3.1–20.7%), 7.8% (95% CI, 6.8–9.0%) and 1.8% (95% CI, 1.3–2.4%) in those without sFGR. Subgroup analyses considering the different indications for delivery (spontaneous *vs* iatrogenic) could not be performed owing to a lack of information in the original studies. PE or gestational hypertension complicated 19.9% (95% CI, 12.4–28.6%) of pregnancies with sFGR and 12.8% (95% CI, 10.4–15.4%) of those without sFGR.

Composite morbidity occurred in 28.2% (95% CI, 7.8–55.1%) of fetuses from pregnancies with sFGR and 13.9% (95% CI, 6.5–23.5%) of those from pregnancies without sFGR. When stratified according to the sFGR status within a twin pair, composite morbidity occurred in 39.0% (95% CI, 11.1–71.5%) of growth-restricted fetuses and 29.9% (95% CI, 3.5–65.0%) of appropriately grown fetuses. An Apgar score of <7 at 5 min was observed in 1.1% (95% CI, 0.0–3.5%) of fetuses from pregnancies with sFGR, while there were insufficient data on this parameter for pregnancies without sFGR. Respiratory morbidity was reported in 18.3% (95% CI, 3.3–41.7%) of fetuses from pregnancies with sFGR and 9.9% (95% CI, 8.1–11.8%) of those from pregnancies without sFGR, while no pooled data synthesis on neurological or infectious morbidity could be performed. Finally, 39.7% (95% CI, 17.4–64.6%) of fetuses from pregnancies with sFGR and 16.3% (95% CI, 8.0–26.7%) of those from pregnancies without sFGR were admitted to the NICU.

We could not perform subgroup analyses according to GA at diagnosis or Doppler status because the original publications did not report this information sufficiently.

Computation of ORs was also affected by the small number of available 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, 5.2 (95% CI, 3.2–8.6)) (Figure 2) and composite morbidity or admission to the NICU (OR, 3.2 (95% CI, 1.9–5.6)) (Figure 3) compared with those not affected by sFGR, while there was no significant difference in the risk of PTB before 34 weeks ($P=0.220$) or PE/gestational hypertension ($P=0.210$) (Table 4). Finally, the risk of PND (OR, 2.1 (95% CI, 1.0–4.1); 27/888 *vs* 13/888; $I^2=0\%$, $P=0.037$, five studies) and composite morbidity (OR, 1.9 (95% CI, 1.7–3.1); 94/218 *vs* 72/218; $I^2=60.7\%$, $P=0.012$, four studies) was higher in the smaller compared with the larger twin.

Table 3 Pooled proportions (PP) for different outcomes explored in systematic review in dichorionic diamniotic (DCDA) twin pregnancies complicated *vs* those not complicated by selective fetal growth restriction (sFGR)

	DCDA complicated by sFGR				*DCDA not complicated by sFGR*			
Outcome	*Studies (n)*	*Cases (n/N)*	*PP (95% CI) (%)*	I^2 *(%)*	*Studies (n)*	*Cases (n/N)*	*PP (95% CI) (%)*	I^2 *(%)*
Intrauterine 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)	98.5	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 (1.26–2.39)	0
Pre-eclampsia/GH	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 min	3	18/1105	1.06 (0.03–3.52)	86.3	1	2/134	—	—
Respiratory morbidity	4	87/759	18.29 (3.25–41.73)	97.0	2	151/1555	9.88 (8.11–11.80)	14.4
Necrotizing enterocolitis	2	2/142	3.88 (0.27–18.84)	64.4	0	—	—	—
Admission to NICU	5	378/978	39.74 (17.42–64.59)	98.0	2	411/2045	16.29 (8.04–26.74)	71.3

No data were available on neurological morbidity, infectious morbidity or retinopathy of prematurity. GH, gestational hypertension; NICU, neonatal intensive care unit.

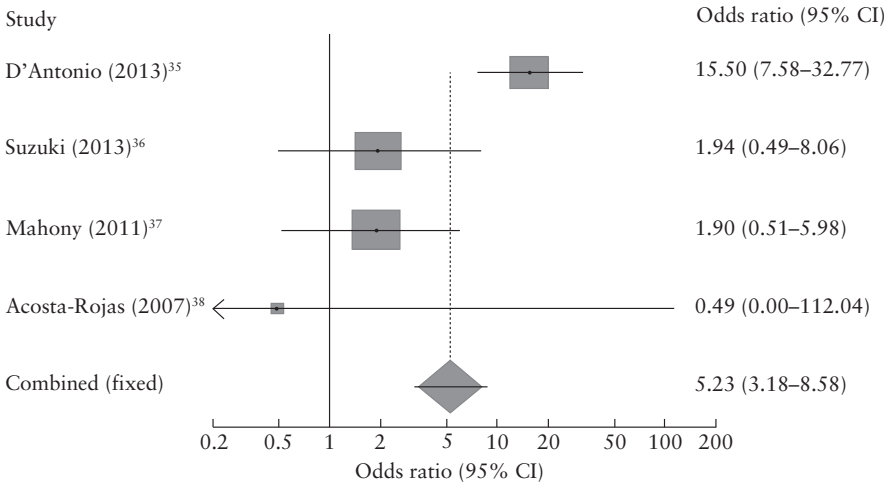

Figure 2 Pooled odds ratio and 95% CI for risk of intrauterine demise in dichorionic diamniotic twin pregnancies complicated *vs* those not complicated by selective fetal growth restriction. Only first author is given for each study.

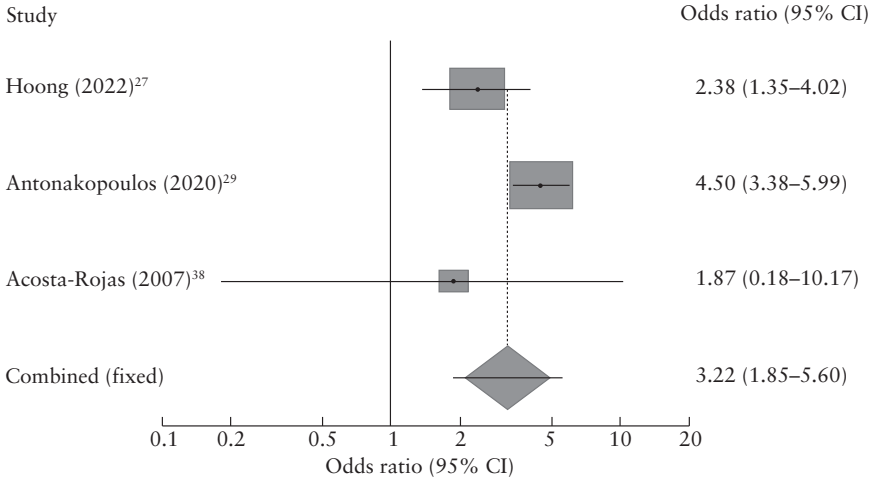

Figure 3 Pooled odds ratio and 95% CI for risk of composite morbidity or admission to neonatal intensive care unit in dichorionic diamniotic twin pregnancies complicated *vs* those not complicated by selective fetal growth restriction. Only first author is given for each study.

Table 4 Pooled odds ratios for outcomes explored in systematic review in dichorionic diamniotic twin pregnancies complicated *vs* those not complicated by selective fetal growth restriction (sFGR)

Outcome	*Studies* (n)	*sFGR* vs *non-sFGR* (n/N)	*Odds ratio (95% CI)*	I^2 *(%)*	P
Intrauterine demise	4	30/1290 *vs* 31/6728	5.23 (3.18–8.58)	81.8	< 0.001
Preterm birth < 34 weeks	2	84/481 *vs* 356/2604	1.61 (0.75–3.46)	76.3	0.220
Pre-eclampsia/gestational hypertension	3	72/397 *vs* 401/2950	1.55 (0.78–3.09)	76.2	0.210
Composite morbidity/admission to NICU	3	156/360 *vs* 540/3405	3.22 (1.85–5.60)	76.2	0.012

NICU, neonatal intensive care unit.

DISCUSSION

Summary of main findings

The findings of this systematic review and meta-analysis provide estimates of perinatal morbidity and mortality in DCDA twin pregnancies complicated by sFGR and quantify the excess risk compared with DCDA twin pregnancies without sFGR. Among the sFGR pregnancies, PND and composite morbidity occurred in 5% and 28% of fetuses, respectively, and approximately 40% of fetuses were admitted to the NICU. The comparative analysis was affected by the smaller number of included studies relative to the main analysis. Overall, we found that DCDA twin pregnancies complicated by sFGR had a 5-fold increased risk of IUD and a 3-fold higher risk of composite morbidity or admission to the NICU compared with those not complicated by sFGR. In our review, the difference in the occurrence of PE and PTB before 34 weeks between DCDA twin pregnancies with and those without sFGR was not significant.

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 does not specifically define sFGR but considers a difference of 15–25% in EFW to indicate discordant fetal growth[40]. Conversely, the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) guidelines on twin pregnancy define sFGR as a condition in which the EFW of one fetus is below the 10th centile and intertwin EFW discordance is ≥ 25%, but state that EFW discordance greater than 20% should prompt increased fetal surveillance[16]. Our findings provide evidence that the incidence of perinatal morbidity and mortality in DCDA twin pregnancies complicated by sFGR is higher than that in DCDA pregnancies without sFGR, which should facilitate risk stratification, antenatal surveillance and tailored counseling of parents.

In our review, we did not find a significant difference in the risk of PE between DCDA twin pregnancies with sFGR and those without sFGR. Caution should be exercised while interpreting this finding. First, we were limited by the number of studies, as only three studies explored this outcome. Second, it was not clear whether these studies had employed singleton or twin-specific reference charts. The literature on the association between PE and FGR in DCDA twin pregnancies is conflicting, and any association depends on the reference charts used for the diagnosis of FGR[41–47]. In studies in which the diagnosis of FGR was based on singleton reference charts, there was no association between FGR and PE, as significantly more twins were classified as FGR[41]. However, in recent studies in which investigators employed twin-specific charts, the association between PE and FGR in twin pregnancies was notable and significant[44,46]. Proctor *et al.*[44] showed that, when using a twin-based reference chart 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 rate of PTB prior to 34 weeks in DCDA twin pregnancies with sFGR compared with those without sFGR. However, similarly to PE, we were limited in our analysis, as only two studies were available 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 analyze the risk of PTB before 32 and before 28 weeks, which we believe would have been more meaningful and clinically informative. Additionally, we could not analyze iatrogenic and spontaneous PTB separately, which is an important consideration, as management of DCDA twin pregnancies with sFGR requires careful decision-making to decrease the risk of iatrogenic prematurity in the normally growing cotwin, while 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 addressed extensively in the published literature. The ISUOG guidelines on twin pregnancy suggest that DCDA twin pregnancies with sFGR should be managed as singleton pregnancies with FGR[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 associated with the presence of, as well as the impact of iatrogenic prematurity on, the normally growing cotwin. Future studies are needed to establish whether a different surveillance and management approach in these pregnancies could improve their perinatal outcome.

The additional information from this systematic review may help parents to understand the actual risk of adverse perinatal outcome and to make decisions about their care that is best suited to them. This review also highlights the lack of largescale prospective studies with high-quality data focusing 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 future research should focus on the stratification of sFGR according to GA at onset and the pattern of discordance over serial scans.

Strengths and limitations

To the best of our knowledge, this is the first systematic review to explore the outcome of DCDA twin pregnancies complicated by sFGR. A thorough literature search and the multitude of outcomes explored represent the main strengths of this review. The retrospective non-randomized design of the included studies, their small sample size, variable definitions of sFGR and lack of stratification of the analysis according to the degree of fetal smallness, Doppler status and GA at diagnosis represent its main weaknesses. Assessment of 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 small number of individual studies, which limits the reliability of formal tests. However, despite its limitations, this study represents the most comprehensive up-to-date review of the published literature on the outcomes of DCDA twin pregnancies complicated by sFGR.

Conclusions

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

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Search strategies

Table S2 Excluded studies and reason for exclusion