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Outcome of monochorionic twin pregnancy with selective intrauterine growth restriction according to umbilical artery Doppler flow pattern of smaller twin: systematic review and meta-analysis

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KEYWORDS: monochorionic twins; outcome; selective intrauterine growth restriction; ultrasound; umbilical Doppler

ABSTRACT

Objective *To explore the outcome of monochorionic twin pregnancies affected by selective intrauterine growth restriction (sIUGR) according to the umbilical artery Doppler pattern of the smaller twin.*

Methods *An electronic search of MEDLINE, EMBASE, CINAHL and ClinicalTrials.gov databases (2000–2016) was performed. sIUGR was defined as the presence of one twin with an estimated fetal weight and/or abdominal circumference < 10^{th} or < 5^{th} percentile and classified according to the umbilical artery Doppler flow pattern of the smaller twin (Type I: persistently positive; Type II: persistently absent/reversed; Type III: intermittently absent/reversed). Primary outcomes were perinatal mortality, intrauterine death, neonatal death and double fetal loss. Secondary outcomes were neonatal morbidity, including abnormal postnatal brain imaging, intraventricular hemorrhage, periventricular leukomalacia, admission to neonatal intensive care unit and respiratory distress syndrome, deterioration of fetal status, gestational age at delivery and degree of birth-weight discordance. A composite adverse outcome, defined as the presence of any mortality or abnormal brain findings, was also assessed. Quality assessment of the included studies was performed using the Newcastle–Ottawa Scale. A random-effects meta-analysis was used to compute the summary odds ratios (ORs), mean differences (MD) and proportions for the different outcomes.*

Results *Thirteen studies (610 pregnancies) were included. The risk of perinatal mortality was higher in twins affected by Type II compared with Type I sIUGR (OR, 4.1 (95% CI, 1.6–10.3)), whereas there was no difference among the other variants of growth restriction. Risk of abnormal postnatal brain imaging was significantly higher in twins affected by either Type II (OR, 4.9 (95% CI, 1.9–12.9)) or Type III (OR, 8.2 (95% CI, 2.0–33.1)) sIUGR compared with Type I sIUGR. The risk for neonatal intensive care unit admission was higher in Type II compared with Type I sIUGR (OR, 18.3 (95% CI, 1.0–339.7)). Twin pregnancies affected by Type I sIUGR were delivered at a significantly later gestational age compared with Type II (MD, 2.8 (95% CI, 1.83–3.86) weeks) and Type III (MD, 2.1 (95% CI, 0.97–3.19) weeks). The degree of birth-weight discordance was higher in Type II compared with Type I (MD, 21.6% (95% CI, 9.9–33.2%)) and Type III (MD, 9.3% (95% CI, 3.8–14.9%)) sIUGR.*

Conclusion *Monochorionic twin pregnancies affected by Type II sIUGR are at a higher risk of perinatal mortality and morbidity compared with Type I. The likelihood of an abnormal outcome is usually not significantly different between sIUGR Types II and III, although the latter has an unpredictable clinical course.*

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INTRODUCTION

Monochorionic (MC) twin pregnancies are at a higher risk of perinatal mortality and morbidity compared with dichorionic twin pregnancies, especially due to twin-to-twin transfusion syndrome (TTTS), selective intrauterine growth restriction (sIUGR) and twin reversed arterial perfusion sequence[1,2]. sIUGR affects about 10–25% of MC twin pregnancies and has been defined classically as the presence of one twin with an estimated fetal weight and/or abdominal circumference $< 10^{th}$ or $< 5^{th}$ percentile[3]. The pathophysiology of sIUGR in MC pregnancies relies not only on the presence of abnormal placental sharing, but also on the magnitude and direction of blood-flow interchange through the placental anastomoses, which, in turn, is the main factor responsible for perinatal outcome, irrespective of fetal weight[4,5].

Gratacós *et al.*[6] proposed a new classification system of sIUGR in MC twins based on the umbilical artery (UA) Doppler flow pattern of the smaller twin. According to this classification, MC twins affected by sIUGR can be divided into three different groups on the basis of the Doppler characteristics of diastolic flow in the UA: Type I (persistently positive), Type II (persistently absent/reversed) and Type III (intermittently absent/reversed). In the original series, Type I sIUGR showed the best outcome in terms of perinatal mortality and morbidity, Type II had the worst prognosis and Type III was characterized by an unpredictable clinical course. The importance of this classification is not only its ability to predict the clinical evolution and outcome of different types of sIUGR, but also its association with placental angioarchitecture[6,7].

Since its introduction, several studies on sIUGR using Gratacós *et al.*'s classification have been published. However, the majority of these studies were small, with different outcome measures, antenatal management and time at follow-up. Counseling of parents based on single small studies that are subject to publication bias may be inadequate. We, therefore, sought to explore, by means of a systematic review, the outcome in MC twin pregnancies affected by sIUGR according to the UA Doppler pattern of the smaller twin.

METHODS

This review was performed according to an *a-priori* designed protocol and recommended for systematic reviews and meta-analyses[8,9]. MEDLINE, CINAHL and EMBASE databases (2000–2016) were searched electronically on 24 July 2016, utilizing combinations of the relevant medical subject heading terms, keywords and word variants for 'selective intrauterine growth restriction', 'ultrasound' and 'outcome' (Table S1). 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[10].

The study was registered with the PROSPERO database (registration number: CRD42016043062).

Study selection

Two authors (D.B., F.D.) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus; full-text copies of those papers were obtained and the same two reviewers extracted relevant data regarding study characteristics and pregnancy outcome independently. Inconsistencies were discussed by the reviewers and consensus reached or by discussion with a third author. 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. For those articles in which information was not reported but the methodology was such that this information would have been recorded initially, the original study authors were contacted.

Quality assessment of the included studies was performed using the Newcastle–Ottawa Scale (NOS)[9]. According to NOS, each study is judged on three broad perspectives: selection of the study groups; comparability of the groups; and ascertainment of the outcome of interest[9]. Assessment of the selection of a study 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 of a study includes evaluation of the comparability of cohorts on the basis of the design or analysis. Finally, ascertainment of the outcome of interest includes evaluation of the type of assessment for the outcome of interest, and length and adequacy of follow-up[9]. According to NOS, a study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability.

sIUGR was defined as the presence of one twin with an estimated fetal weight and/or abdominal circumference $< 10^{th}$ or $< 5^{th}$ percentile and classified according to the UA Doppler flow pattern of the smaller twin (Type I: persistently positive; Type II: persistently absent/reversed; Type III: intermittently absent/reversed)[3,6].

The primary outcomes were perinatal mortality, intrauterine death, neonatal death and double fetal loss. Secondary outcomes were neonatal morbidity, including abnormal postnatal brain imaging, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), admission to the neonatal intensive care unit (NICU) and respiratory distress syndrome (RDS), deterioration of fetal status, gestational age at delivery and degree of birth-weight (BW) discordance. Furthermore, a composite adverse outcome, defined as the presence of any mortality or abnormal brain findings, was also created in order to ascertain the overall burden of adverse outcomes in these pregnancies.

Fetal deterioration was defined as progression of abnormal Doppler findings suggestive of severe hypoxia, defined according to the gestational age at presentation, such as worsening of arterial or anomalous venous Doppler, abnormal heart traces and/or biophysical profile, which required active management[6]. Abnormal brain imaging was defined as the presence of either IVH or PVL. IVH was classified according to the presence and amount of blood in the germinal matrix and lateral ventricles, as demonstrated by cranial ultrasound, and graded as follows: Grade I, only germinal matrix hemorrhage; Grade II, IVH filling 10–50% of the ventricle; Grade III, IVH filling > 50% of the ventricle; Grade IV, hemorrhage in any parenchymal location in addition to unilateral or bilateral IVH[11,12]. PVL was defined as any injury to cerebral white matter occurring in a characteristic distribution and consisting of periventricular focal necrosis, with subsequent cystic formation, and more diffuse cerebral white matter injury[13]. PVL was graded according to the classification proposed by de Vries *et al.*[14]

We planned a sensitivity analysis according to the severity of IVH and PVL; for this, mild IVH was defined as Grade I and II, with severe IVH as at least Grade III; mild and severe PVL were defined as Grade I and at least Grade II, respectively.

Only studies reporting the prenatal diagnosis of sIUGR in MC twins according to the classification of Gratacós *et al.*[6] were considered suitable for inclusion in the systematic review. Cases with superimposed TTTS were not included in the analysis. Studies reporting only one type of sIUGR or those from which the information regarding the type of sIUGR could not be extrapolated were excluded. Studies including exclusively cases undergoing fetal therapy, such as laser coagulation of the placental anastomoses or cord occlusion, were not included. Finally, studies published before 2000 were not included as we considered that advances in prenatal imaging techniques and improvements in the diagnosis and definition of sIUGR in MC twins made these studies less relevant.

Only full-text articles were considered eligible for inclusion. Case reports, conference abstracts and case series with fewer than three cases, irrespective of the fact that the anomaly was isolated or not, were also excluded to avoid publication bias.

Statistical analysis

We used meta-analyses of proportions to combine data[15]. Funnel plots displaying the outcome rate from individual studies *vs* their precision (1/standard error) were carried out with an exploratory aim. Tests for funnel-plot asymmetry were not used when the total number of publications included for each outcome was less than 10. In this case, the power of the tests is too low to distinguish chance from real asymmetry[16,17]. 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 $\geq$ 50% indicate a substantial level of heterogeneity. A random-effects model was used for all meta-analyses. Potential publication bias was formally assessed through Egger's regression asymmetry test.

We evaluated separately the differences between the three classes of sIUGR (Type I *vs* II, I *vs* III and II *vs* III) and between the smaller and larger twin for all outcomes explored. We included observational cohort studies in which: (a) many comparisons reported zero events in one group; (b) several comparisons reported zero events in both groups; (c) exposed and unexposed group sizes were frequently severely unbalanced. In such cases, many of the most commonly used meta-analytical methods, including those using risk difference that could be used to handle zero-event studies, can produce biased estimates when events are rare. Random-effects meta-analyses were used to compute the summary odds ratios (ORs) and mean differences (MD).

StatsDirect 3.0.171 (StatsDirect Ltd, Altrincham, UK) and RevMan 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) statistical software were used to analyze the data.

RESULTS

Study selection and characteristics

In total, 2405 articles were identified, of which 51 were assessed with respect to their eligibility for inclusion (Table S2) and 13 studies[6,18–29] were included in the systematic review (Table 1, Figure 1). These 13 studies included 610 MC twin pregnancies affected by sIUGR (the 81 pregnancies in the earlier study of Ishii *et al.*[29] were not included in this total as they were assumed to overlap with those included in the later study by this group[25], which analyzed different outcomes).

Quality assessment of the included studies was performed using NOS[9] (Table 2). Most of the included studies showed an overall good rate with regard to selection and comparability of the study groups and for ascertainment of the outcome of interest. The main weaknesses of these studies were their retrospective design, small sample size, lack of assessment for most of the outcomes explored, different follow-up times and heterogeneity in prenatal management.

Synthesis of results

Among the 610 MC twin pregnancies included, 39.0% (95% CI, 35.1–43.0%) were classified as Type I, 38.2% (95% CI, 34.3–42.2%) as Type II and 22.8% (95% CI, 19.5–26.3%) as Type III according to the UA Doppler pattern of the smaller twin. The mean gestational age at diagnosis was 26.5 (95% CI, 22.2–30.9) weeks for Type I, 21.1 (95% CI, 19.4–22.8) weeks for Type II and 20.2 (95% CI, 15.2–25.3) weeks for Type III sIUGR.

Table 1 Summary of characteristics of studies included in the systematic review comparing outcomes in monochorionic twin pregnancies with selective intrauterine growth restriction

Reference	*Country*	*Study design*	*Gestational age at ultrasound examination (weeks)**	*Pregnancies* (n)	*Outcome observed*	*Age at follow-up*
Rustico (2017)[18]	Italy	Retrospective	20 (17–22)	140	Mortality, morbidity	24 months (12 months to 7 years)
Pasquini (2015)[19]	Italy	Retrospective	20.8 (15.9–31.4)	42	Mortality, morbidity	NS
Liao (2014)[20]	Brazil	Prospective	29.5 ± 3.1	18	Mortality	NS
Zuckerwise (2015)[21]	USA	Retrospective	NS	10	Mortality	NS
Visentin (2013)[22]	Italy	Prospective	18 (16–20)	24	Mortality, morbidity	NS
Yinon (2014)[23]	Israel	Prospective	NS	15	Mortality	NS
Lopriore (2012)[24]	Netherlands	Retrospective	NS	44	Mortality, morbidity	NS
Ishii (2011)[25]†	Japan	Retrospective	20 (18–25)	101	Mortality, morbidity	NS
Weisz (2011)[26]	Israel	Prospective	NS	37	Mortality	NS
Chang (2010)[27]	Taiwan	Prospective	NS	27	Mortality, morbidity	NS
Machado (2014)[28]	Brazil	Retrospective	35.8 (25–39)	18	Mortality, morbidity	NS
Ishii (2009)[29]†	Japan	Retrospective	NS	81	Morbidity	6 months
Gratacós (2007)[6]	Spain	Prospective	21.7 (16–27)	134	Mortality, morbidity	28 ± 7 days

Only first author of each study is given. *Median (range) or mean ± SD. †For calculation of prevalence of different types of sIUGR, only Ishii (2011)[25], and not Ishii (2009)[29], was considered, to avoid inclusion of duplicate cases. NS, not stated.

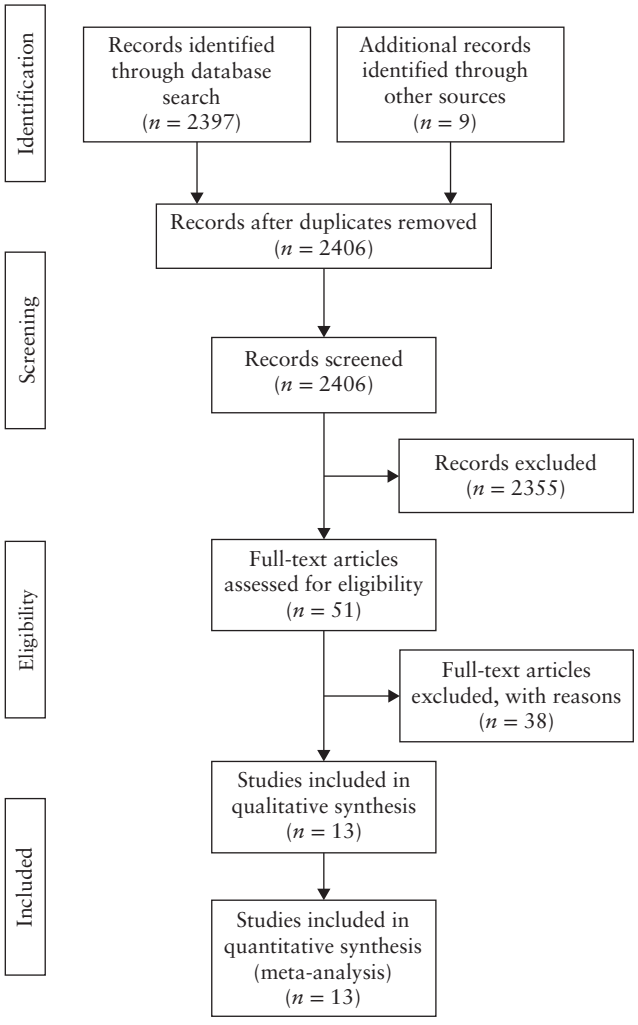

Figure 1 Flowchart summarizing inclusion of studies in the systematic review.

Table 2 Quality assessment of studies included in the systematic review according to the Newcastle–Ottawa Scale

Reference	*Selection*	*Comparability*	*Outcome*
Rustico (2017)[18]	★★	★	★★
Pasquini (2015)[19]	★★	★	★★
Liao (2014)[20]	★★	★	★★
Zuckerwise (2015)[21]	★★	★	★★
Visentin (2013)[22]	★★	★	★★
Yinon (2014)[23]	★★	★	★★
Lopriore (2012)[24]	★★	★	★
Ishii (2011)[25]	★★	★★	★★
Weisz (2011)[26]	★★	★	★★
Chang (2010)[27]	★★	★	★★
Machado (2014)[28]	★★	★	★
Ishii (2009)[29]	★★	★	★
Gratacós (2007)[6]	★★★	★★	★★

Only first author of each study is given. The study can be awarded a maximum of one star for each numbered item within selection and outcome categories and a maximum of two stars for comparability.

Mortality

Overall, perinatal mortality occurred in 4.1% (95% CI, 1.2–8.7%) of twins with Type I, 16.1% (95% CI, 4.6–32.7%) of those with Type II and 11.5% (95% CI, 7.7–16.0%) of those with Type III sIUGR (Table 3, Figure 2). The risk of perinatal mortality was higher in twins affected by Type II compared with Type I sIUGR (OR, 4.1 (95% CI, 1.6–10.3)), whereas there was no difference among the other variants of growth restriction (Table 4). When analyzing separately the risk of mortality in the smaller *vs* larger twin, the occurrence of perinatal mortality was significantly higher in the growth-restricted fetus compared with the larger twin (OR, 2.4 (95% CI, 1.3–4.4)) in Type II sIUGR, whereas there was no difference in Types I and III sIUGR (Table 5).

Table 3 Pooled proportions for outcomes of monochorionic twin pregnancies with selective intrauterine growth restriction (sIUGR), according to type of sIUGR as determined by umbilical artery Doppler flow pattern of smaller twin

Outcome	*Studies (*n*)*	*Fetuses (*n/N*)*	I^2 *(%)*	*Pooled proportion (% (95% CI))*
Type I sIUGR				
Perinatal mortality	8	21/336	57.6	4.13 (1.2–8.7)
Intrauterine death	10	10/404	0	3.07 (1.6–5.0)
Neonatal death	10	12/392	53.7	1.77 (0.3–4.5)
Double fetal loss	10	2/202	0	1.94 (0.5–4.3)
Abnormal brain imaging	6	5/204	58.4	3.82 (0.5–10.0)
Intraventricular hemorrhage	3	0/102	0	0.58 (0.04–2.9)
Periventricular leukomalacia	2	2/96	82.1	3.52 (0.9–20.9)
Admission to NICU	2	10/26	0	39.08 (21.9–57.8)
Respiratory distress syndrome	2	8/26	18	32.66 (14.3–54.3)
Composite adverse outcome	12	22/460	48	4.79 (2.2–8.2)
Type II sIUGR				
Perinatal mortality	8	68/322	90.7	16.07 (4.6–32.7)
Intrauterine death	10	47/356	81.6	10.98 (4.1–20.6)
Neonatal death	10	31/366	71.7	7.14 (2.7–13.5)
Double fetal loss	10	14/180	28.3	7.03 (3.1–12.5)
Abnormal brain imaging	6	27/195	66.4	14.15 (6.7–23.8)
Intraventricular hemorrhage	3	8/97	74.6	8.23 (0.7–22.8)
Periventricular leukomalacia	2	11/79	75.9	15.70 (3.1–35.4)
Admission to NICU	2	43/46	81.7	93.33 (67.8–99.3)
Respiratory distress syndrome	2	21/46	94.5	52.14 (3.4–98.0)
Composite adverse outcome	12	105/400	84.4	23.77 (13.5–35.9)
Type III sIUGR				
Perinatal mortality	7	24/218	0	11.52 (7.7–16.0)
Intrauterine death	9	21/236	0	9.60 (6.2–13.6)
Neonatal death	9	7/260	52.3	4.64 (1.2–10.1)
Double fetal loss	9	4/118	0	4.88 (1.8–9.4)
Abnormal brain imaging	5	23/191	61.3	11.88 (4.6–22.0)
Intraventricular hemorrhage	2	6/123	0	5.43 (2.2–10.1)
Periventricular leukomalacia	1	13/111	—	11.71 (6.4–19.2)
Admission to NICU	1	7/12	—	58.33 (27.7–84.8)
Respiratory distress syndrome	1	11/12	—	91.67 (61.5–99.8)
Composite adverse outcome	11	51/274	65.6	16.28 (8.4–26.1)

NICU, neonatal intensive care unit.

Intrauterine death occurred in 3.1% (95% CI, 1.6–5.0%) of fetuses with Type I sIUGR, whereas the corresponding values for Types II and III were 11.0% (95% CI, 4.1–20.6%) and 9.6% (95% CI, 6.2–13.6%), respectively (Table 3). The risks of intrauterine death (OR, 5.6 (95% CI, 2.7–11.3)) and neonatal death (OR, 4.1 (95% CI, 1.0–16.6)) were significantly higher in Type II compared with Type I sIUGR, whereas there was no difference in their occurrence between Types II and III (Table 4).

Double fetal loss occurred in 1.9% (95% CI, 0.5–4.3%) of Type I, 7.0% (95% CI, 3.1–12.5%) of Type II and 4.9% (95% CI, 1.8–9.4%) of Type III sIUGR. The risk of double fetal loss was significantly higher in Type II compared with Type I sIUGR (OR, 4.8 (95% CI, 1.3–17.4)), whereas there was no difference between the other types.

Morbidity

The occurrence of abnormal brain imaging in MC twin pregnancies affected by sIUGR and stratified according to the UA Doppler of the smaller twin was explored in six studies. Twins affected by Type II (OR, 4.9 (95% CI, 1.9–12.9)) or Type III (OR, 8.2 (95% CI, 2.0–33.1)) sIUGR had a significantly higher risk of abnormal postnatal brain imaging compared with Type I sIUGR (Table 4, Figure 3). There was no difference in risk for an abnormal postnatal brain scan in the growth-restricted compared with the larger twin for all sIUGR types (Table 5).

The prevalence of IVH in Types I, II and III sIUGR was 0.6% (95% CI, 0.04–2.9%), 8.2% (95% CI, 0.7–22.8%) and 5.4% (95% CI, 2.2–10.1%), whereas the corresponding values for PVL were 3.5% (95% CI, 0.9–20.9%), 15.7% (95% CI, 3.1–35.4%) and 11.7% (95% CI, 6.4–19.2%), respectively. When considering only IVH Grade III or more, there was no case of IVH in Types I (1.7% (95% CI, 0.3–9.8%); two studies[22,28]; 0/26; I^2, 0%) or II (1.0% (95% CI, 0.2–5.9%); two studies[22,28]; 0/46; I^2, 0%), whereas there was only one case of IVH Grade III in a growth-restricted twin affected by Type III sIUGR (8.3% (95% CI, 0.2–38.5%)) as reported by Machado *et al.*[28].

The risk of IVH (OR, 10.6 (95% CI, 1.1–102.6)) and PVL (OR, 4.4 (95% CI, 1.0–18.5)) was significantly higher in Type II compared with Type I sIUGR, whereas there was no increased risk in either IVH or PVL in Type II compared with Type III.

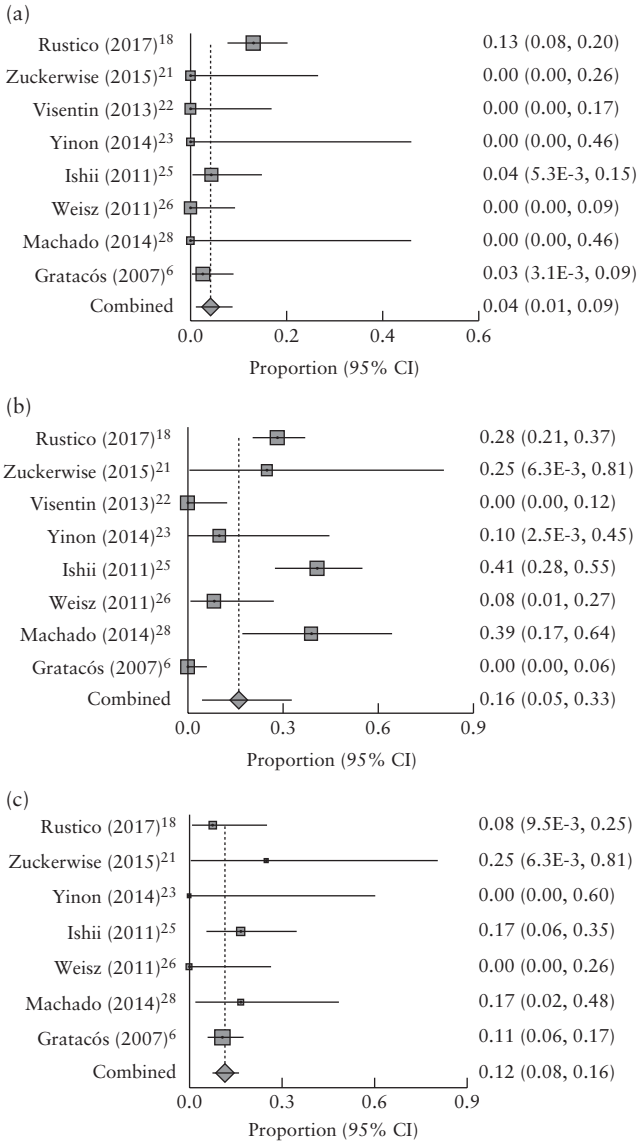

Figure 2 Pooled proportions for prevalence of perinatal mortality in monochorionic twin pregnancies with Type I (a), Type II (b) and Type III (c) selective intrauterine growth restriction. Only first author of each study is given.

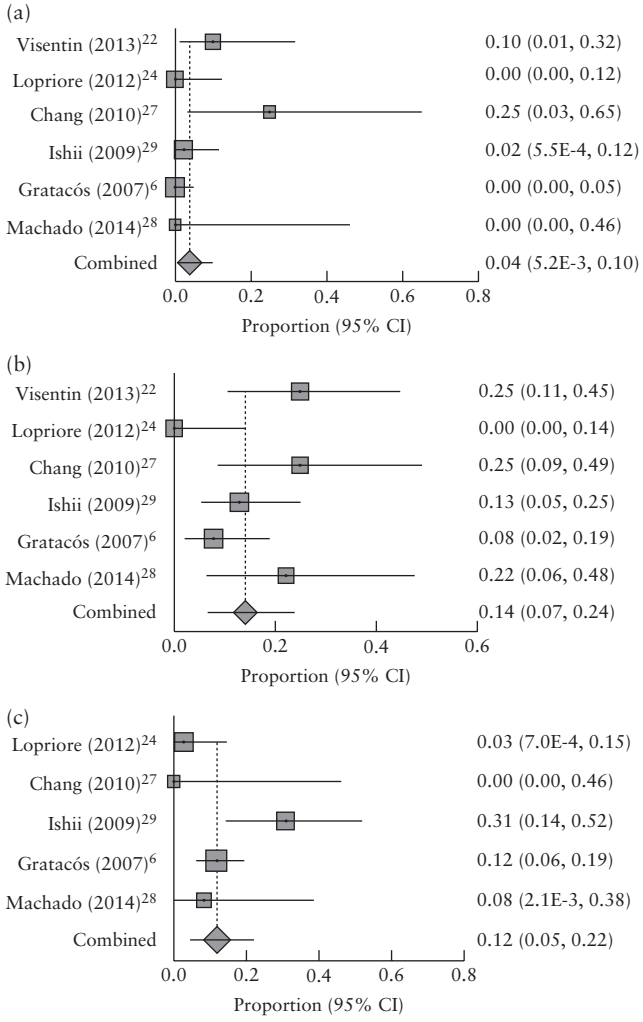

Figure 3 Pooled proportions for prevalence of abnormal brain imaging in monochorionic twin pregnancies with Type I (a), Type II (b) and Type III (c) selective intrauterine growth restriction. Only first author of each study is given.

Only two studies assessed the prevalence and risk of NICU admission and RDS in MC twin pregnancies affected by sIUGR. The prevalence of NICU admission in Types I, II and III sIUGR was 39.1% (95% CI, 21.9–57.8%), 93.3% (95% CI, 67.8–99.3%) and 58.3% (95% CI, 27.7–84.8%), respectively. The risk of NICU admission was higher in Type II compared with Type I sIUGR (OR, 18.3 (95% CI, 1.0–339.7)), whereas there was no difference between Type II *vs* III and Type I *vs* III sIUGR. The risk of NICU admission and RDS was not different between the smaller and larger twins for all sIUGR types (Table 5).

The risk of a composite adverse outcome, defined as the presence of any mortality and abnormal brain finding, was higher in Type II (OR, 4.9 (95% CI, 2.9–8.3)) and Type III (OR, 5.1 (95% CI, 1.7–14.9)) compared with Type I sIUGR, whereas there was no difference between Types II and III sIUGR (Table 4, Figure 4).

Deterioration of fetal status, gestational age at delivery and BW discordance

Deterioration of fetal status occurred in 16.2% (95% CI, 3.6–35.5%) of Type I, 58.9% (95% CI, 33.9–81.7%) of Type II and 10.1% (95% CI, 4.9–16.9%) of Type III sIUGR twins. The risk of deterioration was higher in Type II compared with Type I (OR, 7.2 (95% CI, 1.7–29.8)) and Type III (OR, 16.1 (95% CI, 1.5–168.0)), whereas there was no difference in risk in Type I *vs* III sIUGR. The mean gestational age at delivery in Types I, II and III sIUGR was 33.7 (95% CI, 33.0–34.3) weeks, 30.9 (95% CI, 30.0–31.8) weeks and 32.0 (95% CI, 31.3–32.8) weeks. Twin pregnancies affected by Type I sIUGR were delivered at a significantly later gestational age than those with Type II (MD 2.8 (95% CI, 1.8–3.9) weeks; $P < 0.001$) and Type III (MD, 2.1 (95% CI, 1.0–3.2) weeks; $P < 0.001$), whereas there was no difference in gestational age at delivery between Types II and III sIUGR (MD, −0.9 (95% CI, −1.9 to 0.2) weeks; $P = 0.09$).

Table 4 Pooled odds ratios for outcomes in monochorionic twin pregnancies with selective intrauterine growth restriction (sIUGR), according to type of sIUGR as determined by umbilical artery Doppler flow pattern of smaller twin

Outcome	*Studies (n)*	*Fetuses (n/N)*	I^2 *(%)*	*Pooled odds ratio (95% CI)*
Perinatal mortality				
Type I *vs* Type II	8	21/336 *vs* 68/322	26.7	4.12 (1.6–10.3)
Type II *vs* Type III	7	68/294 *vs* 24/218	26.1	2.51 (0.97–6.5)
Type I *vs* Type III	7	21/316 *vs* 24/218	23.7	2.54 (0.9–7.0)
Intrauterine death				
Type I *vs* Type II	10	10/404 *vs* 47/356	0	5.56 (2.7–11.3)
Type II *vs* Type III	9	47/328 *vs* 21/236	22.1	1.92 (0.7–5.1)
Type I *vs* Type III	9	10/384 *vs* 21/236	0	3.34 (1.3–8.4)
Neonatal death				
Type I *vs* Type II	10	12/392 *vs* 31/366	41.2	4.08 (1.0–16.6)
Type II *vs* Type III	9	31/338 *vs* 7/260	0	1.87 (0.7–4.6)
Type I *vs* Type III	9	12/372 *vs* 7/260	4.9	2.07 (0.6–7.7)
Double fetal loss				
Type I *vs* Type II	10	2/202 *vs* 14/180	0	4.80 (1.3–17.4)
Type II *vs* Type III	9	14/166 *vs* 4/118	0	2.34 (0.4–12.5)
Type I *vs* Type III	9	2/192 *vs* 4/118	15	0.39 (0.02–8.6)
Abnormal brain imaging				
Type I *vs* Type II	6	5/204 *vs* 23/191	0	4.93 (1.9–12.9)
Type II *vs* Type III	5	20/167 *vs* 23/191	17.8	0.66 (0.3–1.6)
Type I *vs* Type III	5	3/184 *vs* 23/191	0	8.21 (2.0–33.1)
Intraventricular hemorrhage				
Type I *vs* Type II	3	0/102 *vs* 8/97	0	10.56 (1.1–102.6)
Type II *vs* Type III	2	8/69 *vs* 6/123	0	2.08 (0.6–6.7)
Type I *vs* Type III	2	0/82 *vs* 6/123	0	5.82 (0.5–68.0)
Periventricular leukomalacia				
Type I *vs* Type II	2	2/96 *vs* 11/79	0	4.40 (1.0–18.5)
Type II *vs* Type III	1	4/51 *vs* 13/111	—	0.61 (0.2–2.1)
Type I *vs* Type III	1	0/76 *vs* 13/111	—	∞ (2.6–∞)
Admission to NICU				
Type I *vs* Type II	2	10/26 *vs* 43/46	66.3	18.25 (1.0–339.7)
Type II *vs* Type III	1	15/18 *vs* 7/12	—	3.41 (0.5–28.6)
Type I *vs* Type III	1	3/6 *vs* 7/12	—	0.73 (0.1–7.9)
Respiratory distress syndrome				
Type I *vs* Type II	2	8/26 *vs* 21/46	52.9	1.72 (0.3–9.9)
Type II *vs* Type III	1	15/18 *vs* 11/12	—	0.45 (0.04–5.0)
Type I *vs* Type III	1	3/6 *vs* 11/12	—	0.11 (0.001–1.9)
Composite adverse outcome				
Type I *vs* Type II	12	27/460 *vs* 105/400	8.1	4.87 (2.9–8.3)
Type II *vs* Type III	12	98/372 *vs* 51/274	40.4	1.40 (0.6–3.1)
Type I *vs* Type III	11	25/440 *vs* 51/274	44.7	5.06 (1.7–14.9)

NICU, neonatal intensive care unit.

The degree of BW discordance was 23.0% (95% CI, 14.7–31.4%) in Type I, 44.3% (95% CI, 36.8–51.8%) in Type II and 32.5% (95% CI, 28.5–36.6%) in Type III sIUGR. Twins affected by Type II sIUGR had a significantly higher degree of BW discordance than those with Type I (MD, 21.6% (95% CI, 9.9–33.2%)) and Type III (MD, 9.3% (95% CI, 3.8–14.9%)) sIUGR; both $P < 0.001$.

DISCUSSION

Main findings

The findings from this systematic review show that MC twin pregnancies affected by Type II sIUGR are at a higher risk of perinatal mortality and morbidity compared with those with Type I, whereas the likelihood of an abnormal outcome is usually not significantly different between Types II and III, although Type III sIUGR is affected by an unpredictable clinical course. The prevalence of abnormal postnatal brain imaging and admission to NICU at birth are higher in Type II compared with Type I sIUGR. Pregnancies affected by Types II and III sIUGR are delivered at a significantly earlier gestational age than those affected by Type I and those with Type II have a higher degree of BW discordance compared with Types I and III.

Study limitations

The small number of cases in some of the included studies, their retrospective non-randomized design, heterogeneity in prenatal management and different periods of follow up represent the major limitations of this systematic review. Most of the observed outcomes were reported by only a limited proportion of the included studies and we could not stratify the analysis according to different

Table 5 Pooled proportions and odds ratios for outcomes in monochorionic twin pregnancies with selective intrauterine growth restriction (sIUGR), according to type of sIUGR, for smaller and larger fetuses

		Smaller fetus			*Larger fetus*			*Smaller* vs *larger fetus*	
Outcome	*Studies* (n)	n/N	I^2 (%)	*Pooled proportion* (% (95% CI))	n/N	I^2 (%)	*Pooled proportion* (% (95% CI))	I^2 (%)	*Odds ratio* (95% CI)
Type I sIUGR									
Perinatal mortality	8	13/168	32	6.37 (2.3–12.2)	8/168	0	5.64 (2.7–9.6)	0	1.72 (0.7–4.4)
Intrauterine death	10	6/202	0	4.30 (2.0–7.5)	4/202	57.6	4.13 (1.2–8.7)	0	1.44 (0.4–5.0)
Neonatal death	12	8/196	24	3.30 (0.9–7.0)	4/196	0	2.75 (1.0–5.5)	0	2.14 (0.6–7.5)
Abnormal brain imaging	6	2/102	0	2.78 (0.5–6.8)	3/102	30.4	3.67 (0.5–9.5)	0	0.80 (0.1–4.7)
Intraventricular hemorrhage	3	0/51	0	1.14 (0.08–5.8)	0/51	0	1.14 (0.08–5.8)	0	—
Periventricular leukomalacia	2	1/48	64.7	3.84 (0.7–21.2)	1/48	64.7	3.84 (0.7–21.2)	—	1 (0.1–18.6)
Admission to NICU	2	6/13	0	46.39 (21.9–71.8)	4/13	0	33.04 (11.8–58.8)	0	1.93 (0.4–9.8)
Respiratory distress syndrome	2	6/13	0	46.39 (21.9–71.8)	2/13	0	18.43 (3.3–42.1)	0	5.23 (0.7–37.6)
Composite adverse outcome	12	16/230	16.5	6.59 (3.4–10.7)	11/230	0	5.38 (2.8–8.6)	0	1.56 (0.7–3.5)
Type II sIUGR									
Perinatal mortality	8	45/161	85.8	24.78 (8.5–46.1)	23/161	73.2	9.25 (2.0–21.0)	0	2.44 (1.3–4.4)
Intrauterine death	10	29/178	68.5	14.42 (5.9–25.9)	18/178	47.3	9.19 (3.8–16.6)	0	1.76 (0.9–3.7)
Neonatal death	10	23/183	66.9	12.08 (4.6–22.4)	8/183	0	4.88 (2.3–8.4)	0	2.58 (1.1–5.9)
Abnormal brain imaging	6	18/93*	58	19.54 (8.7–33.4)	9/102	48.7	9.38 (2.9–18.9)	30.6	1.96 (0.6–6.2)
Intraventricular hemorrhage	3	5/44*	52.5	11.50 (1.7–28.5)	3/53	46.7	6.84 (0.5–19.6)	0	2.11 (0.4–10.6)
Periventricular leukomalacia	2	10/35*	79.6	30.95 (4.8–66.9)	1/44	0	3.58 (0.2–10.9)	0	9.53 (1.5–60.2)
Admission to NICU	2	22/23	36.6	94.15 (77.1–100)	21/23	71.5	90.43 (58.8–99.5)	—	2.29 (0.2–31.0)
Respiratory distress syndrome	2	13/23	60.2	58.42 (27.1–86.4)	8/23	96	36.63 (13.5–98.9)	74.3	2.90 (0.1–145.3)
Composite adverse outcome	2	70/200	76.8	34.45 (20.7–49.7)	35/200	67.6	14.25 (6.4–24.6)	0	2.60 (1.6– 4.4)
Type III sIUGR									
Perinatal mortality	7	17/109	0	16.56 (10.3–24.0)	7/109	0	7.26 (3.2–12.8)	0	2.37 (0.95–5.9)
Intrauterine death	9	17/118	0	15.62 (9.8–22.6)	4/118	0	4.88 (1.8–9.4)	0	3.44 (1.3–8.8)
Neonatal death	9	3/130	28.3	3.86 (0.7–9.6)	4/130	20	4.43 (0.96–10.2)	3.9	0.99 (0.2–4.5)
Abnormal brain imaging	5	5/90*	49.3	7.52 (1.2–18.5)	18/101	43.5	16.34 (6.7–29.1)	21.8	0.35 (0.1–1.3)
Intraventricular hemorrhage	2	4/56*	2.8	8.22 (2.3–17.2)	2/67	0	3.97 (0.7–9.9)	0	2.17 (0.4–10.9)
Periventricular leukomalacia	1	1/50*	—	2.0 (0.1–10.6)	12/61	—	19.67 (10.6–31.8)	—	0.08 (0.01–0.7)
Admission to NICU	1	3/6	—	50.00 (11.8–88.2)	4/6	—	66.67 (22.3–95.7)	—	0.50 (0.05–5.2)
Respiratory distress syndrome	1	5/6	—	83.33 (35.9–99.6)	6/6	—	100 (54.1–100)	—	0.28 (0.01–8.4)
Composite adverse outcome	11	25/137	51.2	19.57 (9.7–31.9)	23/137	55	12.38 (4.4–23.6)	26.1	1.29 (0.5–3.4)

*Some smaller fetuses died *in utero* and/or did not have postnatal brain imaging and were not included in the analysis. NICU, neonatal intensive care unit.

gestational ages at presentation of sIUGR, type of UA flow abnormality (absent *vs* reversed end-diastolic flow) and different subtypes of neuromorbidity. Furthermore, it was not possible to explore the outcome when there was progression of Doppler anomalies.

The management of twins affected by sIUGR is based on expert opinion and this, in turn, has a profound influence on the occurrence of any adverse perinatal outcome. Early delivery may prevent mortality but is associated with a higher burden of short- and long-term morbidity. In this scenario, the data reported in this systematic review should be interpreted with caution, as they may be largely affected by the different management protocols in place at each center, rather than reflecting the natural history of the condition.

Implications for clinical practice

Management of sIUGR in MC twin pregnancy is challenging. There are no randomized controlled trials on how to manage and when to deliver these pregnancies. Furthermore, the natural history and clinical evolution of sIUGR in MC twins have not yet been ascertained completely, precluding an evidence-based approach to their management in clinical practice.

Classification of sIUGR based on the UA Doppler flow pattern of the smaller twin provides a valuable tool to stratify the obstetric risk of these pregnancies. However, it may not reflect entirely the natural history of the anomaly because management choices, such as fetal therapy, can affect perinatal outcome. Therefore, the different types of sIUGR may not reflect accurately progression of disease severity.

Type I sIUGR most likely represents the milder spectrum of growth restriction in MC twins; the degree of unequal placental sharing between the twins is smaller than for the other types of sIUGR, thus precluding a large discrepancy in fetal size. Furthermore, the relatively small number of arterioarterial anastomoses compared with the other sIUGR types allows relative hemodynamic stability between the twins, which is reflected in the lower occurrence of perinatal death and postnatal brain damage[30–33]. In the absence of Doppler abnormalities, it seems reasonable to follow up these pregnancies conservatively with weekly ultrasound scans[33].

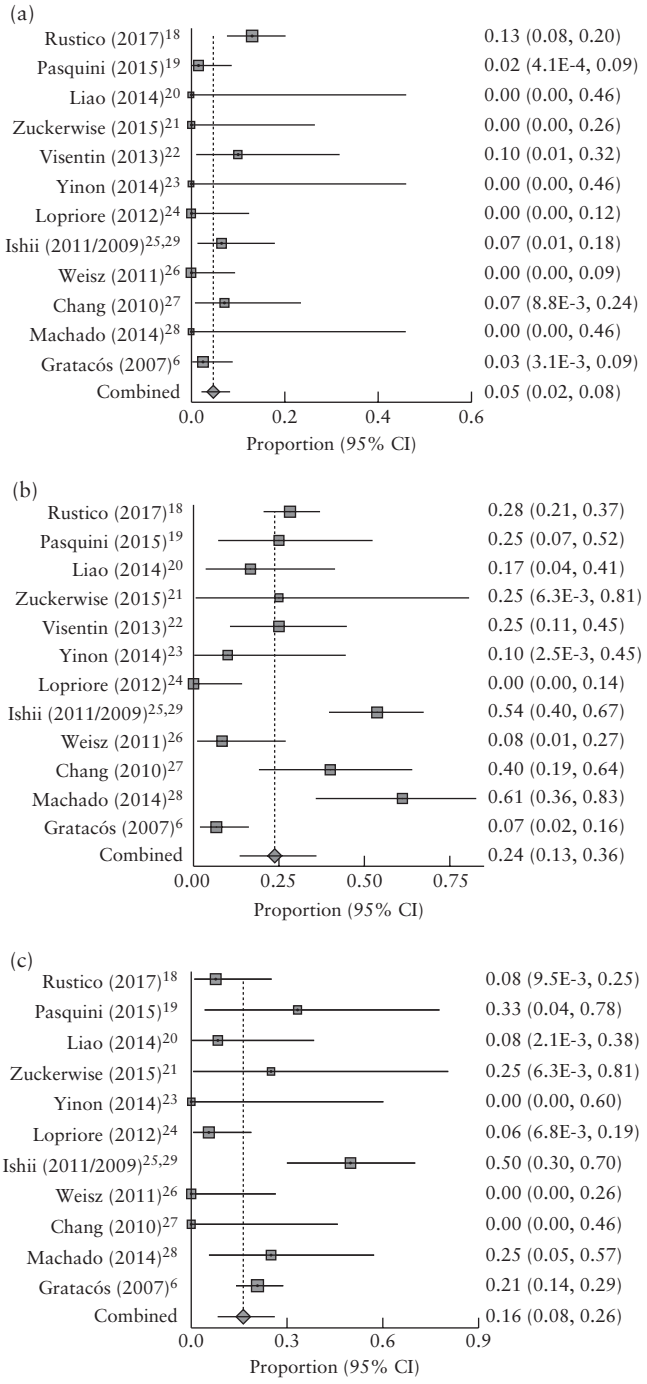

Figure 4 Pooled proportions for prevalence of composite adverse outcome in monochorionic twin pregnancies with Type I (a), Type II (b) and Type III (c) selective intrauterine growth restriction. Only first author of each study is given.

Type II sIUGR pregnancies are affected commonly by severe discordance in fetal weight and by progressive abnormalities in arterial and venous Doppler, requiring delivery at an earlier gestational age. However, the latency between onset of UA flow anomalies and delivery is usually longer than that in singleton and dichorionic twin gestations[34]. Type II sIUGR is usually characterized by a progressive deterioration of fetal status, requiring early delivery. The optimal prenatal management of these pregnancies is yet to be established and should be tailored according to the gestational age at diagnosis, the degree of fetal weight discordance and the severity of Doppler abnormalities. A closer follow up with biweekly scans in the presence of absent or reversed end-diastolic flow in the UA, followed by delivery when venous Doppler abnormalities occur, represents the most reasonable option, although it would require confirmation in a prospective trial.

Prenatal therapy, such as cord occlusion or laser coagulation of placental anastomoses, can be considered before viability but it is affected by a relatively high rate of cotwin loss or maternal complications, such as preterm delivery, and is technically more difficult than when performed for TTTS[35,36].

Type III sIUGR is characterized by the presence of intermittent absent or reversed end-diastolic flow in the UA of the smaller twin. This feature is unique to MC twins and is due to the peculiar vascular arrangement of Type III sIUGR placentae, which show significantly more large arterioarterial anastomoses compared with uncomplicated Types I and II sIUGR twins[37,38]. These large arterioarterial anastomoses allow continuous blood exchange between the umbilical cords of the twins, which is reflected in a specific appearance of the UA waveform. The intermittent Doppler pattern is mostly seen close to the placental insertion site of the umbilical cord and can be missed easily unless low sweep speed pulsed Doppler is used. The clinical course of pregnancies with Type III sIUGR is mainly determined by the magnitude and direction of blood exchange, which may lead to different clinical outcomes, even in twins showing the same degree of growth discrepancy.

Type III sIUGR is affected by a high rate of unexpected fetal demise, even in the case of stable Doppler findings, thus questioning the actual role of Doppler ultrasound in managing these pregnancies. Management of Type III sIUGR is arbitrary; several factors such as gestational age at diagnosis, degree of growth discordance and severity of Doppler anomalies may help the decision planning, but parents should be counseled about the unpredictable clinical course of these pregnancies. Fetal therapy may be considered before viability although, as for Type II sIUGR, it may be challenging technically due to the short distance between the umbilical cord and the absence of twin oligohydramnios–polyhydramnios sequence[39].

Large multicenter prospective trials are needed to find the optimal management of these pregnancies according to gestational age at diagnosis and type and severity of UA Doppler pattern and degree of BW discordance.

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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 strategy for PubMed, EMBASE and CINAHL

Table S2 Excluded studies and reasons for exclusion

This article has been selected for Journal Club.

A slide presentation, prepared by Dr Yael Raz, one of UOG's Editors for Trainees, is available online.

Chinese translation by Dr Yang Fang. Spanish translation by Dr Ruben Dario Fernandez.

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Resultado del embarazo de gemelos monocoriónicos con restricción selectiva del crecimiento intrauterino según el patrón de flujo Doppler de la arteria umbilical del gemelo más pequeño: revisión sistemática y metaanálisis

RESUMEN

Objetivo Explorar el resultado de los embarazos de gemelos monocoriónicos afectados por una restricción selectiva del crecimiento intrauterino (RCIUs) según el patrón Doppler de la arteria umbilical del gemelo más pequeño.

Métodos Se llevó a cabo una búsqueda en las bases de datos electrónicas MEDLINE, EMBASE, CINAHL y ClinicalTrials.gov (2000–2016). La RCIUs se definió como la presencia de un gemelo con un peso fetal estimado y/o circunferencia abdominal <10° o <5° percentil y clasificado de acuerdo con el patrón de flujo Doppler de la arteria umbilical del gemelo más pequeño (onda de Tipo I: persistentemente positiva; Tipo II: persistentemente ausente/reversa; Tipo III: intermitentemente ausente/reversa). Los resultados primarios fueron la mortalidad perinatal, la muerte intrauterina, la muerte neonatal y la pérdida de ambos fetos. Los resultados secundarios fueron la morbilidad neonatal, incluyendo una imagen postnatal anómala del cerebro, la hemorragia intraventricular, la leucomalacia periventricular, el ingreso a la unidad de cuidados intensivos neonatales y el síndrome de dificultad respiratoria, el deterioro del estado fetal, la edad gestacional al momento del parto y el grado de discordancia con el peso al nacer. También se evaluó un resultado adverso compuesto, definido como la presencia de cualquier mortalidad o hallazgos de anomalías en el cerebro. La evaluación de calidad de los estudios incluidos se realizó mediante la escala Newcastle-Ottawa. Para el cálculo del resumen de las razones de momios (RM), las diferencias de medias (DM) y las proporciones para los diferentes resultados, se utilizó un metaanálisis de efectos aleatorios.

Resultados Se incluyeron trece estudios (610 embarazos). El riesgo de mortalidad perinatal fue mayor en gemelos afectos por las RCIUs del Tipo II, en comparación con las de Tipo I (RM 4,1 (IC 95%, 1,6–10,3)), mientras que no hubo diferencia entre las otras variantes de restricción del crecimiento. El riesgo de imágenes cerebrales posnatales anómalas fue significativamente mayor en gemelos afectos por RCIUs de Tipo II (RM 4,9 (IC 95%, 1,9–12,9)) o Tipo III (RM 8,2 (IC 95%, 2,0–33,1)), en comparación con las RCIUs de Tipo I. El riesgo de ingreso a la unidad de cuidados intensivos neonatales fue mayor en el Tipo II, en comparación con las RCIUs de Tipo I (RM 18,3 (IC 95%, 1,0–339,7)). El parto de los embarazos de gemelos afectados por las RCIUs de Tipo I sucedió a una edad gestacional significativamente más tardía, en comparación con los de Tipo II (DM 2,8 semanas (IC 95%, 1,83–3,86)) y de Tipo III (DM 2,1 semanas (IC 95%, 0,97–3,19)). El grado de discordancia con el peso al nacer fue mayor en el Tipo II, en comparación con las RCIUs de Tipo I (DM 21,6% (IC 95%, 9,9–33,2%)) y de Tipo III (DM 9,3% (IC 95%, 3,8–14,9%)).

Conclusión Los embarazos de gemelos monocoriónicos afectos de RCIUs de Tipo II tienen un mayor riesgo de mortalidad y morbilidad perinatal en comparación con las de Tipo I. La probabilidad de un resultado anómalo no suele ser significativamente diferente entre las RCIUs de los tipos II y III, aunque este último tipo tiene un desarrollo clínico impredecible.

根据双胎中小胎的脐动脉多普勒血流频谱确定单绒毛膜双胎妊娠选择性宫内生长受限的结局：系统评价和 meta 分析

目的：探讨根据双胎中小胎的脐动脉多普勒频谱确定发生选择性宫内生长受限（selective intrauterine growth restriction，sIUGR）的单绒毛膜双胎妊娠的结局。

方法：计算机检索 MEDLINE、EMBASE、CINAHL 和 ClinicalTrials.gov 数据库（2000–2016 年）。将 sIUGR 定义为双胎中一胎估计胎儿体重和/或腹围<第 10 个或<第 5 个百分位数，并根据双胎中小胎的脐动脉多普勒血流频谱分类（Ⅰ类，持续正向；Ⅱ类，持续缺失/反向；Ⅲ类：间断缺失/反向）。主要结局为围产期死亡、胎死宫内、新生儿死亡和双胎死亡。次要结局为新生儿发病（包括出生后脑部影像异常、脑室内出血、脑室周围白质软化症、入住新生儿重症监护室和呼吸窘迫综合征）、胎儿状态恶化、分娩孕周及出生体重不均衡程度。还对综合不良结局进行评估，即出现死亡或脑部检查结果异常。采用 Newcastle-Ottawa 量表对纳入的研究进行质量评估。采用随机效应 meta 分析计算总比值比（odds ratios，ORs）、均差及不同结局的比例。

结果：纳入 13 项研究（610 例孕妇）。与Ⅰ类 sIUGR 相比，Ⅱ类 sIUGR 双胎的围产期死亡风险较高[OR，4.1（95% CI，1.6~10.3）]，而其他生长受限变量两组间无差异。与Ⅰ类 sIUGR 相比，Ⅱ类[OR，4.9（95% CI，1.9~12.9）]或Ⅲ类[OR，8.2（95% CI，2.0~33.1）] sIUGR 双胎出生后脑部影像异常风险明显较高。与Ⅰ类 sIUGR 相比，Ⅱ类 sIUGR 入住新生儿重症监护室的风险较高[OR，18.3（95% CI，1.0~339.7）]。Ⅰ类 sIUGR 双胎妊娠的分娩孕周明显晚于Ⅱ类[MD，2.8（95%CI，1.83~3.86）周]或Ⅲ类[MD，2.1（95%CI，0.97~3.19）周]。与Ⅰ类[MD，21.6%（95%CI，9.9%~33.2%）]和Ⅲ类[MD，9.3%（95%CI，3.8%~14.9%）] sIUGR 相比，Ⅱ类出生体重不均衡程度较大。

结论：与Ⅰ类 sIUGR 相比，Ⅱ类 sIUGR 单绒毛膜双胎妊娠的围产期死亡和发病风险较高。Ⅱ类和Ⅲ类 sIUGR 相比，异常结局的发生概率通常无统计学差异，尽管Ⅲ类 sIUGR 的临床病程不可预测。