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REVIEW

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Gestational age at birth and outcome in monochorionic twins with different types of selective fetal growth restriction: A systematic literature review

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Abstract

This systematic review aims to assess the gestational age at birth and perinatal outcome [intrauterine demise (IUD), neonatal mortality and severe cerebral injury] in monochorionic twins with selective fetal growth restriction (sFGR), according to Gratacós classification based on umbilical artery Doppler flow patterns in the smaller twin. Seventeen articles were included. Gestational age at birth varied from 33.0 to 36.0 weeks in type I, 27.6–32.4 weeks in type II, and 28.3–33.8 weeks in type III. IUD rate differed from 0%–4% in type I to 0%–40% in type II and 0%–23% in type III. Neonatal mortality rate was between 0%–10% in type I, 0%–38% in type II, and 0%–17% in type III. Cerebral injury was present in 0%–2% of type I, 2%–30% of type II and 0%–33% of type III cases. The timing of delivery in sFGR varied substantially among studies, particularly in type II and III. The quality of evidence was moderate due to heterogenous study populations with varying definitions of sFGR and perinatal outcome parameters, as well as a lack of consensus on the use of the Gratacós classification, leading to substantial incomparability. Our review identifies the urgent need for uniform antenatal diagnostic criteria and definitions of outcome parameters.

Key points

What is already known about this topic?

- Selective fetal growth restriction (sFGR) with abnormal umbilical artery Doppler flow patterns in the smaller twin (type II and III) is associated with poor perinatal outcome.
- International consensus on optimal antenatal and perinatal management is lacking. Whether timing of delivery and gestational age (GA) at birth varies between international centers is not well known.

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What does the study add?

- GA at birth in sFGR twins varies substantially between international centers, especially in type II and III: type I = 33.0–36.0 weeks, type II = 27.6–32.4 weeks and type III = 28.3–33.8 weeks.
- Fetal and neonatal mortality rates were highest in type II and type III. Cerebral injury was present in 2%–30% in type II and 0%–33% in type III cases.
- Our review identifies the urgent need for uniform antenatal diagnostic criteria, definitions of outcome parameters and standardized long-term follow-up in sFGR.

1 | INTRODUCTION

Selective fetal growth restriction (sFGR), defined as estimated fetal weight (EFW) of one twin <10th centile and an EFW discordance >25%, is a complication affecting 10%–15% of monochorionic (MC) twin pregnancies resulting in an intertwin growth discordance.[1] The pathophysiology is primarily due to unequal placental sharing, in which the growth-restricted twin has a smaller share of the placenta leading to suboptimal growth.[2] sFGR is associated with high perinatal morbidity and mortality rates.[3] Even if both twins are born alive, there is still a risk of neurological impairment due to increased rates of prematurity.

The extent of the perinatal morbidity and mortality risk depends on the type of sFGR. sFGR can be classified into three types according to Gratacós.[4] Type I is characterized by a continuous positive end-diastolic flow in the umbilical artery (UA) of the smaller twin and is generally associated with a relatively good outcome.[1–4] Type II is distinguished by a persistently absent or reversed EDF (A/REDF) in the UA and is associated with increased perinatal mortality and morbidity.[1–4] Lastly, type III is characterized by an intermittent absent/reversed EDF (iA/REDF) in the UA and has an unpredictable clinical course due to a large arterio-arterial anastomosis on the placenta, resulting in an unstable and fluctuating blood flow between the fetuses.[1–4]

The current management of sFGR consists mainly of expectant management including fetal monitoring and medically induced preterm birth in case of fetal distress. In some cases, fetal interventions may be considered, including selective feticide using cord occlusion or fetoscopic laser coagulation (FLC). However, management in sFGR is not based on robust evidence, but mainly on expert opinion. Hence, uncertainty regarding the optimal management strategy still persists. sFGR twins are often delivered electively at an early gestational age (GA) due to the fear of intrauterine demise (IUD). Preterm birth is in turn associated with an increased risk of adverse neonatal outcomes. The balance between the risk of IUD and the risk of adverse neonatal outcomes following prematurity remains a clinical dilemma. Due to a lack of robust evidence to guide a consensus regarding the optimal GA at birth for these infants, the practice varies across fetal medicine centers.

To evaluate the international variation in the GA at birth in sFGR twins and to gain more understanding of worldwide differences in perinatal outcome in sFGR pregnancies, we performed a systematic review and studied the differences in GA at birth in twin pregnancies complicated by sFGR according to the Gratacós classification.

2 | METHODS

2.1 | Search strategy

This systematic review was conducted according to PRISMA guidelines.[5] An information specialist was involved in the development of the search terms. The online electronic PubMed database, EMBASE, Web of Science and Cochrane Library was searched in June 2022 by using the Boolean combination of: "Fetal Growth Retardation" AND "Twins, Monozygotic" AND "Gestational Age". Additionally, a variety of synonyms were added as free text words and MESH terms (Appendix). A publication date restriction was applied to select studies published between 2007, the year the Gratacós classification was introduced, and 2022. Lastly, reference lists of reviewed articles were manually searched to identify relevant missed articles.

2.2 | Study selection

All articles were assessed for eligibility through screening of the title and abstract. Subsequently, the full text was evaluated. Articles (clinical trials, cohort studies and case-control studies, both prospective and retrospective in nature) were eligible for inclusion when the cohort consisted of MC twin pregnancies complicated by sFGR, classified into the three Gratacós types and expectantly managed. Articles were excluded when they did not distinguish between isolated sFGR and sFGR with twin-twin transfusion syndrome (TTTS) and/or twin anemia polycythemia sequence (TAPS).[6,7] Additionally, articles were excluded when FLC or selective reduction were the only management options. Further exclusion criteria were case reports, case series ($N < 3$), reviews, editorials, conference abstracts and unavailable full text. To identify eligibility of inclusion, two reviewers (S.E., S.G.) independently assessed the search results and discrepancies were resolved through discussion.

The primary outcome was GA at birth in the three types of sFGR, as reported in the various cohorts. The secondary outcomes were IUD, neonatal mortality and severe cerebral injury. Definitions of sFGR and delivery indications were reported when present. In order

to compare the various cerebral injuries described in the articles, one definition was formulated. Severe cerebral injury was defined as the presence of intraventricular hemorrhage ≥ grade II, periventricular leukomalacia ≥ grade II, porencephalic cysts and/or intra-parenchymal bleeding.

2.3 | Quality assessment

The "Users Guides to the Medical Literature" and the "GRADE working group" method were used to assess the validity of the included articles with regards to the research question and the overall quality of evidence.[8,9] The validity assessment is based on two primary and two secondary guides. The primary guides were whether there was a representative and well-defined sample at a similar point in the course of disease and whether the follow-up was sufficient and complete. The secondary guides were whether objective and unbiased outcome criteria were used and whether there was adjustment for important prognostic factors. The overall quality of evidence was determined based on the four key elements reported by the "GRADE working group": study design, study quality (in this case the validity assessment), consistency and directness.

3 | RESULTS

The search strategy yielded 723 results. After excluding duplicates, 434 abstracts were screened. The primary assessment led to the exclusion of 399 articles based on above-mentioned inclusion and exclusion criteria. Manual search of the reference lists provided one additional article. Of the remaining 35 articles, 18 were excluded after full text assessment, resulting in a total of 17 articles to be included in this systematic review (Figure 1). The methodology of the studies is presented in Table 1. The study characteristics and neonatal outcomes of sFGR twins with type I, II and III are presented in Tables 2–4, respectively. The mean or median GA at birth in the three subgroups varied greatly per cohort and is shown in Figure 2. The results for all sFGR types are described separately here below.

In summary, the included studies were all published between 2007 and 2021 (mainly after 2016). The majority of studies (10/17) were conducted in Europe, and the others in North/South-America and Asia. Thirteen studies were retrospective and four prospective. All studies focused on MC twin pregnancies diagnosed with sFGR in the absence of TTTS or TAPS, with 6/17 focusing on all management options and 11/17 on expectant management. 7/17 studies reported on all sFGR types and at least two secondary outcomes.

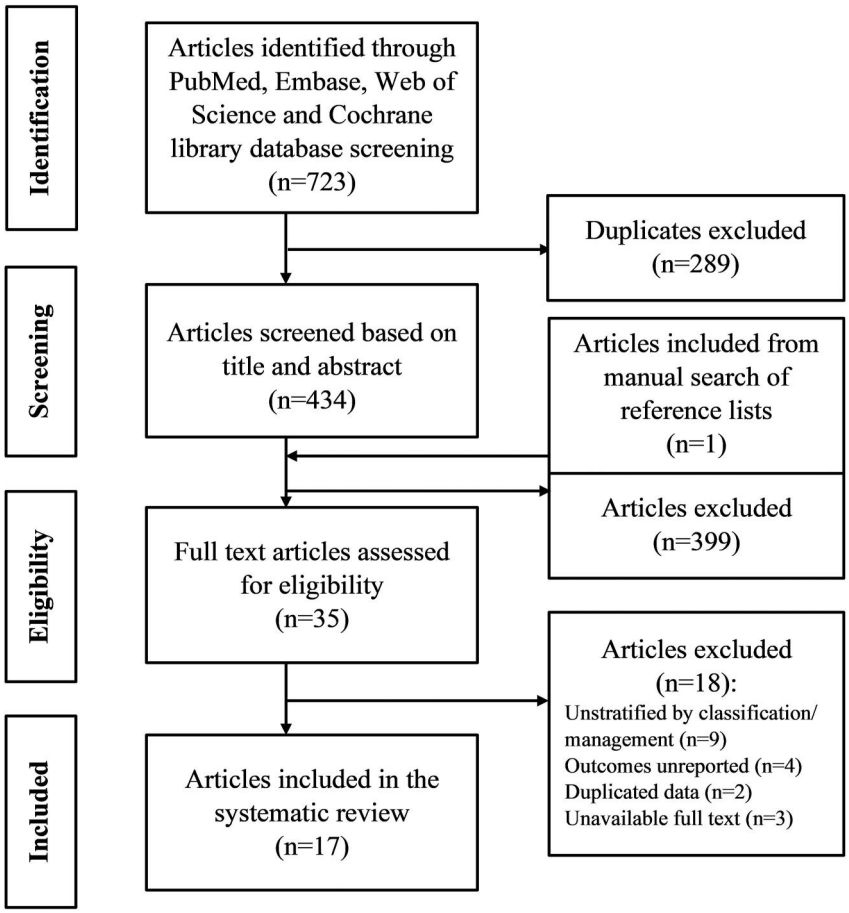

FIGURE 1 Flowchart of study inclusion

TABLE 1 Methodology and validity of included studies

First author, year	Study design	Population	Total sFGR cases	Inclusion criteria	Exclusion criteria	Validity
Gratacós, 2007[4]	Prospective	Spain, Belgium, 2003–2006	*n* = 134 Type I: 39, type II: 30 (21 EM/9 CO), type III: 65 (61 EM/4 CO)	MC twins diagnosed with sFGR at 18–26 weeks in 1/3 participating centers	Signs of TTTS	Adequate
Gratacós, 2008[10]	Retrospective	Spain, Belgium, 2003–2006	*n* = 49 Type III: 49 (31 EM/18 FLC)	MC twins diagnosed with sFGR in 1/3 participating centers	-	Adequate
Ishii, 2009[11]	Retrospective	Japan, 2001–2008	*n* = 63 Type I: 23, Type II: 27, Type III: 13	MC twin pregnancies diagnosed with sFGR <23 weeks' gestation in three centers	Cases with TTTS or the diagnosis of fetal malformation at the time of initial diagnosis	Adequate
Weisz, 2011[12]	Prospective	Israel, 2004–2008	*n* = 37 Type I: 19, type II/III: 18	MC twin pregnancies >24 weeks of gestation followed at single tertiary center	Cases with TTTS or major fetal anomalies	Adequate
Visentin, 2013[13]	Prospective	Italy, 2008–2011	*n* = 14 Type II: 14	MCDA pregnancies with sFGR diagnosed during the first trimester at the clinic or during the second trimester when referred from other centers	Unknown last menstrual period and chorionicity, triplet pregnancy, TTTS or related conditions, MCMA twin pregnancies, and structural or chromosomal abnormalities in either twin	Low
Rustico, 2017[14]	Retrospective	Italy, 2004–2012	*n* = 140 Type I: 65, Type II: 62, Type III: 13	MCDA pregnancies complicated by sFGR examined <26 weeks' gestation at a single tertiary referral center	-	Adequate
Koch, 2017[15]	Retrospective	France, 2008–2015	*n* = 25 Type I: 16, Type II/III: 9	MCDA pregnancies presenting with sFGR >16 weeks' gestation at multiple referral centers	TTTS, TAPS, chromosomal or structural anomalies and IUD at time of diagnosis	Low
Miyadahira, 2018[16]	Retrospective	Brazil, 2007–2016	*n* = 67 Type II: 36 (6 EM/30 FLC) Type III: 31 (22 EM/9 FLC)	MCDA pregnancies with sFGR type II or III diagnosed <26 weeks' gestation and managed at one of the participating centers, with a cervical length of ≥15 mm	TTTS or TAPS	Adequate
Groene, 2019[17]	Retrospective	The Netherlands, 2002–2018	*n* = 83 Type I: 28, Type II: 24, Type III: 31	MC pregnancy placentas with a BW discordance >25% and/or an EFW in one twin <10th centile, consecutively examined at a single tertiary referral center	Co-existing TTTS or TAPS, no record of UA Doppler classification, incomplete placental data, inadequate placental measurements on digital pictures and single or double IUD when severe placental maceration made measurements impossible	Adequate
Quintero, 2019[18]	Prospective	USA,	*n* = 20 Type II: 20 (6 EM/14 FLC)	Surviving MCDA children diagnosed with sFGR between 16 and 26 weeks of gestation, balanced karyotype, no major congenital anomalies, ≥24 months corrected age (±6 weeks) and ≤7 years and 11 months	Refusion of neurodevelopmental assessment and examination, unable to complete the measures in English or Spanish, and families lost to follow up	Low
Sukhwani, 2019[19]	Retrospective	Spain, 2012–2018	*n* = 55 Type I: 25, Type II/III: 30 *Excluded due to peripheral delivery: 11*	MC twin pregnancies diagnosed with sFGR at a single tertiary center	-	Adequate

TABLE 1 (Continued)

First author, year	Study design	Population	Total sFGR cases	Inclusion criteria	Exclusion criteria	Validity
Chon, 2019[20]	Retrospective	USA, 2006–2017	*n* = 48 Type III: 22, Type II or TTTS: 26	MCDA pregnancies referred to a single tertiary center for the evaluation of possible TTTS or sFGR	Cases with both twins having an EFW <10th percentile (dual sFGR)	Adequate
Colmant, 2020[21]	Retrospective	France, 2011–2016	*n* = 108 Type II: 108 (45 EM/50 CC/13 FLC)	MC pregnancies referred to a single center for sFGR with A/REDF (type II) <27 weeks' gestation	Co-existing TTTS and morphological or chromosomal abnormalities detected prenatally	Adequate
Batsry, 2020[22]	Retrospective	Israel, 2012–2018	*n* = 88 (60 EM/28 CO) Type I: 26, Type II: 22, Type III: 12	MCDA pregnancies complicated by sFGR <24 weeks' gestation, managed at a single tertiary referral center	TTTS, TAPS and fetal anomalies, including chromosomal abnormalities or genetic abnormalities	Adequate
Couck, 2020[23]	Retrospective	Belgium, 2002–2018	*n* = 177 Type I: 110, Type II: 11, Type III: 33, subsequent TTTS: 17 *Excluded due to developing TAPS: 6*	MCDA twin pregnancies followed from the first trimester onward and diagnosed with sFGR at 16, 20 or 30 weeks' gestation	MCDA twin pregnancies referred in the first trimester for an anomaly or invasive testing. MCDA twin pregnancies with no available ultrasound data. Pregnancies with single or double demise, TTTS, TAPS, TOP, miscarriage or birth and lethal anomalies diagnosed between the first trimester and 16 weeks, between 16–20 weeks and 20–30 weeks.	High
Shinar, 2021[24]	Retrospective	Canada, China, The Netherlands, Belgium, Israel, Switzerland, 2008–2019	*n* = 328 Type III: 328 *18 pregnancies progressed to TTTS with 7 cases requiring FLC*	MCDA pregnancies complicated by sFGR type III, irrespective of GA at referral or diagnosis, at nine tertiary fetal medicine centers	Higher-order multiple gestations, major fetal structural or genetic anomalies, missing neonatal data, TTTS, TAPS or TRAP sequence at first presentation	High
Aquino, 2021[25]	Retrospective	Brazil, 2010–2018	*n* = 75 Type I: 67, Type II: 5, Type III: 3	MCDA pregnancies affected by sFGR managed expectantly at two referral centers	TTTS (aside from Quintero I), TAPS, congenital anomalies, aneuploidies, genetic syndromes diagnosed during prenatal care or after birth, dual FGR and peripheral institution delivery	Adequate

Abbreviations: A/REDF, absent or reversed end-diastolic flow; BW, birthweight; CC, cord coagulation; CO, cord occlusion; EFW, estimated fetal weight; EM, expectant management; FLC, fetoscopic laser coagulation; IUD, intrauterine demise; MCDA, monochorionic diamniotic; MCMA, monochorionic monoamniotic; sFGR, selective fetal growth restriction; TAPS, twin anemia polycythemia sequence; TOP, termination of pregnancy; TRAP, twin reversed arterial perfusion; TTTS, twin to twin transfusion syndrome; UA, umbilical artery.

TABLE 2 Study characteristics, gestational age at birth and secondary outcomes in twin pregnancies complicated by sFGR type I

First author, year	Patients	Definition sFGR	GA at birth in weeks	IUD	Neonatal mortality	Severe cerebral injury	Delivery indication	Comments
Gratacós, 2007	*n* = 39	EFW <10th centile in one twin	35.4 (16–38)§	2/78 (3) - Smaller: 1/39 (3) - Larger: 1/39 (3) - Double: 1/39 (3)	-	IVH/PVL on neonatal cUS: 0/39 (0)	-	-
Ishii, 2009	*n* = 23	EFW <10th percentile in the smaller twin	36 (26–38)†	2/46 (4) - Smaller: 1/23 (4) - Larger: 1/23 (4) - Double: 0/23 (0)	0/44 (0)	Neurological morbidity:1/44 (2) - Smaller: 1/22 (5) - Larger: 0/22 (0)	Fetal deterioration: 4/23 Growth arrest: 3/23 Spontaneous/maternal indication: 20/23	*Neurological morbidity was defined as IVH Grade III/IV, cystic PVL, blindness and deafness.* *Variety of postnatal cerebral imaging: both cUS and MRI.*
Weisz, 2011	*n* = 19	EFW <10th percentile in one twin	35 (32–37)†	0/38 (0)	0/38 (0)	IVH/PVL on neonatal cUS: 0/38 (0)	-	-
Rustico, 2017	*n* = 65	EFW <10th centile in the smaller twin or EFW discordance ≥25% in the absence of TTTS and TAPS	33 (31–35)†	5/130 (4) - Smaller: 3/65 (5) - Larger: 2/65 (3) - Double: 2/65 (3)	12/118 (10) - Smaller: 8/57 (14) - Larger: 4/61 (7)	-	-	*Three cases of BCC (no larger twins lost), one TOP (both twins lost) and one miscarriage were included in the analysis.*
Koch, 2017	*n* = 16	EFW <10th centile for one of the twins	33.9 (±2.9)‡	0/32 (0)	0/32 (0)	-	-	-
Groene, 2019	*n* = 28	BW discordance >25% and/or an EFW in one twin <10th centile	34.3 (32.7–35.9)†	2/56 (4)[a] - Smaller: 1/28 (4) - Larger: 1/28 (3) - Double: 1/28 (3)	1/52 (2)[a] - Smaller: 1/26 (4) - Larger: 0/26 (0)	Severe cerebral injury on neonatal cUS: 0/39 (0)[a]	-	*Severe cerebral injury was defined as PVL ≥ grade II, IVH ≥ grade III, ventricular dilatation, arterial or venous infarct or other injuries.*
Sukhwani, 2019	*n* = 19	EFW of one twin <10th centile and EFW discordance >25% in the absence of TTTS	35.0 (±1.7)‡	0/38 (0)	0/38 (0)	PVL: 0/38 (0)	-	*Grade of PVL and cerebral imagining modality not reported.*
Batsry, 2020	*n* = 26	EFW of one twin <10th centile or EFW discordance ≥25% in the absence of TTTS or TAPS	34.8 (33.1–35.7)†	0/52 (0)	0/52 (0)	Severe brain lesions on fetal MRI: 0/52 (0)	-	*Severe brain lesions were defined as IVH Grade III/IV, PVL or intraparenchymal hemorrhage.*
Couck, 2020	*n* = 108	EFW <3rd centile in one twin or at least two of the following: - EFW of one twin <10th centile, - AC of one twin <10th centile, - EFW discordance ≥25%, - UA PI of the smaller twin >95th centile	34.6 (32.5–36.1)†	4/216 (2)[a] - Smaller: 2/108 (2) - Larger: 2/108 (2) - Double: 2/108 (2)	0/210 (0)[a]	-	-	*Two pregnancies underwent intervention (1 CO, 1 FLC) and these were included in the analysis of GA at birth. One miscarriage was included in this cohort.*

TABLE 2 (Continued)

First author, year	Patients	Definition sFGR	GA at birth in weeks	IUD	Neonatal mortality	Severe cerebral injury	Delivery indication	Comments
Aquino, 2021	$n = 67$	EFW <3rd centile in one twin or at least two of the following: - EFW of one twin <10th centile, - AC of one twin <10th centile, - EFW discordance ≥25%, - UA PI of the smaller twin >95th centile	34.3 (±2.4)‡	0/134 (0)	1/134 (1) - Smaller: 1/67 (1) - Larger: 0/67 (0)	Severe cerebral injury on neonatal cUS: 0/134 (0)	-	*Severe cerebral injury was defined as IVH grade III/IV, PVL grade II/III or porencephalic cysts.*

Note: Data are presented as median (interquartile range)†, mean (± standard deviation)‡, mean (min-max)§ or *n*/N (%).

Abbreviations: AC, abdominal circumference; BCC, bipolar cord coagulation; BW, birthweight; CO, cord occlusion; cUS, cerebral ultrasound; EFW, estimated fetal weight; FLC, fetoscopic laser coagulation; GA, gestational age; IUD, intrauterine demise; IVH, intraventricular hemorrhage; MRI, magnetic resonance imaging; PI, pulsality index; PVL, periventricular leukomalacia; sFGR, selective fetal growth restriction; TAPS, twin anemia polycythemia sequence; TOP, termination of pregnancy; TTTS, twin to twin transfusion syndrome; UA, umbilical artery.

[a]Authors have been approached for additional data.

3.1 | Quality assessment and level of evidence

The validity of the included studies with regards to our primary research question is presented in Table 1. Three studies were deemed to have a low validity: the study by Visentin et al., the study by Koch et al. and the study by Quintero et al. This was primarily due to their different research questions focusing on, respectively, cord insertion and FLC in sFGR as a treatment option, resulting in only a small population that could be included in this review. Moreover, Visentin et al. solely included sFGR diagnosed in the first trimester and did not fully define their outcome measures. Reported outcomes by Koch et al. were combined for type II and III and cases with IUD at time of diagnosis were excluded, leading to a potential underestimation of mortality. Twelve out of the fourteen other studies were considered to have adequate validity, primarily due to either small study populations, sole inclusion of early-onset sFGR or limited availability of the outcomes of interest in this review. The two studies with high validities, Couck et al. and Shinar et al., presented the largest cohorts diagnosed with sFGR irrespective of GA with the most complete perinatal outcome data.

Overall, the definitions of sFGR and the application of the Gratacós classification differed substantially among studies. While six of the studies defined sFGR as an EFW <10th centile in the smaller twin and/or EFW discordance ≥25%, eight studies only focused on an EFW of one twin <10th centile, one study focused on an abdominal circumference <5th centile and EFW <10th centile (Colmant et al.) and two studies used the new Delphi consensus definition (Couck et al. and Aquino et al., Tables 2–4). Moreover, there was no uniformity in the application of the Gratacós classification and reported outcome measures. This resulted in heterogenous methodologies, and thereby incomparability between studies. Hence, the overall quality of evidence of the included articles for our research question was of moderate quality, suggesting that further research is necessary to provide evidence of superior quality.

3.2 | sFGR type I

Ten cohort studies assessing the GA at birth in sFGR type I were included, with the number of pregnancies per cohort ranging from 16 to 108 (Table 2).

3.2.1 | GA at birth

Based on the included literature, sFGR type I cases were born at a GA between 33.0 and 36.0 weeks' gestation. The lowest GA at birth presented in the type I cohort of Rustico et al. ($n = 65$), which had a median GA at birth of 33 (31–35) weeks.[14] Ishii et al. ($n = 23$) reported the highest median GA at birth of 36 (26–38) weeks.[11] Only 1/10 studies described indication of delivery. The cohort of Ishii et al.

TABLE 3 Study characteristics, gestational age at birth and secondary outcomes in twin pregnancies complicated by sFGR type II

First author, year	Patients	Definition sFGR	GA at birth in weeks	IUD	Neonatal mortality	Severe cerebral injury	Delivery indication	Comments
Ishii, 2009	*n* = 27	EFW <10th percentile in the smaller twin	28 (18–40)†	14/54 (26) - Smaller: 8/27 (30) - Larger: 6/27 (22) - Double: 4/27 (15)	8/40 (20) - Smaller: 5/19 (26) - Larger: 3/21 (14)	Neurological morbidity: 7/40 (18) - Smaller: 4/19 (21) - Larger: 3/21 (14)	Fetal deterioration: 9/27 Growth arrest: 3/27 Double IUD: 4/27 Miscarriage: 2/27 Spontaneous/maternal indication: 8/27	*Neurological morbidity was defined as IVH Grade III/IV, cystic PVL, blindness and deafness.* *Variety of postnatal cerebral imaging: both cUS and MRI.*
Visentin, 2013	*n* = 14	EFW <10th percentile in one twin	30 (28–34)†	0/28 (0)	0/28 (0)	Neonatal cUS: IVH ≥ grade III: 0/28 (0) PVL: 45%	IUD/abnormal biophysical profile/fetal indications: 14/14	*Grade of PVL and proportion of neonates with PVL not reported.*
Rustico, 2017	*n* = 62	EFW <10th centile in the smaller twin or EFW discordance ≥25% in the absence of TTTS and TAPS	30 (27–33)†	22/124 (18) - Smaller: 14/62 (23) - Larger: 8/62 (13) - Double: 8/62 (13)	13/78 (17) - Smaller: 8/31 (26) - Larger: 5/47 (11)	-	-	*Fifteen cases of BCC (four larger twins lost) and three TOP (two both twins and one larger twin lost) were included in the analysis.*
Miyadahira, 2018	*n* = 6	EFW of one twin <10th centile and intertwin EFW discordance ≥25%	32.43 (26.71–37)†	4/12 (33) - Smaller: 3/6 (50) - Larger: 1/6 (17) - Double: 1/6 (17)	3/8 (38) - Smaller: 2/3 (67) - Larger: 1/5 (20)	IVH ≥ grade III:1/6 (17) - Smaller: 0/1 (0) - Larger: 1/5 (20)	Fetal distress: 19/27 Preterm labor: 2/27 IUD: 4/27 Spontaneous: 2/27	*Indication of birth is combined for sFGR type II and III.* *Cerebral imaging modality not reported.*
Groene, 2019	*n* = 24	BW discordance >25% and/or an EFW in one twin <10th centile	31.2 (28.4–34.0)†	6/48 (13)[a] - Smaller: 4/24 (17) - Larger: 2/24 (8) - Double: 2/24 (8)	2/42 (5)[a] - Smaller: 2/20 (10) - Larger: 0/22 (0)	Severe cerebral injury on neonatal cUS: 1/43 (2)[a] - Smaller: 0/19 (0) - Larger: 1/22 (5)	-	*Severe cerebral injury was defined as PVL ≥ grade II, IVH ≥ grade III, ventricular dilatation, arterial or venous infarct or other injuries.*
Quintero, 2019	*n* = 6	EFW <10th percentile in one twin	27.6 (26.7–31.3)†	0/12 (0)	2/12 (17) - Smaller: 2/6 (33) - Larger: 0/6 (0)	IVH Grade III/IV: 3/10 (30) - Smaller: 1/4 (25) - Larger: 2/6 (33)	A/REDF: 2/6 Non-reassuring fetal testing: 3/6 PPROM: 1/6	*Cerebral imaging modality not reported.*

TABLE 3 (Continued)

First author, year	Patients	Definition sFGR	GA at birth in weeks	IUD	Neonatal mortality	Severe cerebral injury	Delivery indication	Comments
Colmant, 2020	*n* = 45	AC <5th centile and EFW <10th centile	32 (30–34)†	11/90 (12) - Smaller: 8/45 (18) - Larger: 3/45 (7)	4/74 (5)	-	-	*One TOP (larger twin) and two cases of miscarriage were included in the analysis.*
Batsry, 2020	*n* = 22	EFW of one twin <10th centile or intertwin EFW discordance ≥25% in the absence of TTTS or TAPS	30.3 (28.6–32.1)†	2/44 (5) - Smaller: 1/22 (5) - Larger: 1/22 (5) - Double: 1/22 (5)	1/42 (2) - Smaller: 1/21 (5) - Larger: 0/21 (0)	Severe brain lesions on fetal MRI: 2/37 (5) - Smaller: 2/18 (11) - Larger: 0/19 (0)	-	*Severe brain lesions were defined as IVH Grade III/IV, PVL or intraparenchymal hemorrhage.*
Couck, 2020	*n* = 5	EFW <3rd centile in one twin or at least two of the following: - EFW of one twin <10th centile, - AC of one twin <10th centile, - EFW discordance ≥25%, - UA PI of the smaller twin >95th centile	30.0 (26.5–38.0)†	4/10 (40)[a] - Smaller: 2/5 (40) - Larger: 2/5 (40) - Double: 2/5 (40)	0/6 (0)[a]	-	-	*Six pregnancies underwent intervention (3 CO, 2 FLC, 1 RFA) and these were included in the analysis of GA at birth.*
Aquino, 2021	*n* = 5	EFW <3rd centile in one twin or at least two of the following: - EFW of one twin <10th centile, - AC of one twin <10th centile, - EFW discordance ≥25%, - UA PI of the smaller twin >95th centile	27.8 (±0.8)‡	0/10 (0)	0/10 (0)	IVH Grade III on neonatal cUS:1/10 (10) - Smaller: 1/5 (20) - Larger: 0/5 (0)	-	*Severe cerebral injury was defined as IVH grade III/IV, PVL grade II/III or porencephalic cysts.*

Note: Data are presented as median (interquartile range)†, mean (± standard deviation)‡, mean (min-max)§ or *n*/N (%).

Abbreviations: A/REDF, absent or reversed end-diastolic flow; AC, abdominal circumference; BCC, bipolar cord coagulation; BW, birthweight; CO, cord occlusion; cUS, cerebral ultrasound; EFW, estimated fetal weight; FLC, fetoscopic laser coagulation; GA, gestational age; IUD, intrauterine demise; IVH, intraventricular hemorrhage; MRI, magnetic resonance imaging; PI, pulsality index; PPROM, preterm premature rupture of membranes; PVL, periventricular leukomalacia; RFA, radiofrequency ablation; sFGR, selective fetal growth restriction; TAPS, twin anemia polycythemia sequence; TOP, termination of pregnancy; TTTS, twin to twin transfusion syndrome; UA, umbilical artery.

[a]Authors have been approached for additional data.

TABLE 4 Study characteristics, gestational age at birth and secondary outcomes in twin pregnancies complicated by sFGR type III

First author, year	Patients	Definition sFGR	GA at birth in weeks	IUD	Neonatal mortality	Severe cerebral injury	Delivery indication	Comments
Gratacós, 2008	*n* = 31	EFW <10th centile in one twin in the absence of severe TTTS	31.0 (26.0–33.0)†	9/62 (15) - Smaller: 6/31 (19) - Larger: 3/31 (10) - Double: 3/31 (10)	-	IVH: 3/53 (6) - Smaller: 1/25 (4) - Larger: 2/28 (7) PVL: 4/53 (8) - Smaller: 0/25 (0) - Larger: 4/28 (14)	-	*Delivery was performed electively at 32 weeks after maternal administration of corticosteroid therapy for fetal maturation.* *Cerebral brain imaging performed on neonatal cUS.*
Ishii, 2009	*n* = 13	EFW <10th percentile in the smaller twin	31 (25–37)†	2/26 (8) - Smaller: 2/13 (15) - Larger: 0/13 (0) - Double: 0/13 (0)	3/24 (13) - Smaller: 0/11 (0) - Larger: 3/13 (23)	Neurological morbidity: 8/24 (33) - Smaller: 3/11 (27) - Larger: 5/13 (38)	Fetal deterioration: 8/13 Growth arrest: 1/13 Spontaneous/ maternal indication: 4/13	*Neurological morbidity was defined as IVH Grade III/IV, cystic PVL, blindness and deafness.* *Variety of postnatal cerebral imaging: both cUS and MRI.*
Rustico, 2017	*n* = 13	EFW <10th centile in the smaller twin or EFW difference ≥25% in the absence of TTTS and TAPS	32 (30–33)†	1/26 (4) - Smaller: 1/13 (8) - Larger: 0/13 (0)	1/21 (5) - Smaller: 1/9 (11) - Larger: 0/12 (0)	-	-	*Two cases of BCC (smaller twin lost) and one TOP (both twins lost) were included in the analysis.*
Miyadahira, 2018	*n* = 22	EFW of one twin <10th centile and intertwin EFW discordance ≥25%	32.85 (27.71–37.71)†	6/44 (14) - Smaller: 4/22 (18) - Larger: 2/22 (9) - Double: 2/22 (9)	1/38 (3) - Smaller: 1/18 (6) - Larger: 0/20 (0)	IVH ≥ grade III:1/32 (3) - Smaller: 1/15 (7) - Larger: 0/17 (0)	Fetal distress: 19/27 Preterm labor: 2/27 IUD: 4/27 Spontaneous: 2/27	*Indication of birth is combined for sFGR type II and III.* *Cerebral imaging modality not reported.*
Groene, 2019	*n* = 31	BW discordance >25% and/or an EFW in one twin <10th centile	31.4 (28.8–34.1)†	4/62 (6)[a] - Smaller: 2/31 (6) - Larger: 2/31 (6) - Double: 2/31 (6)	3/58 (5)[a] - Smaller: 1/29 (3) - Larger: 2/29 (7)	Severe cerebral injury on neonatal cUS: 2/47 (4)[a] - Smaller: 0/23 (0) - Larger: 2/24 (8)	-	*Severe cerebral injury was defined as PVL ≥ grade II, IVH ≥ grade III, ventricular dilatation, arterial or venous infarct or other injuries.*
Chon, 2019	*n* = 22	EFW of one twin <10th centile	33.8 (28.1–37.0)†	1/44 (2) - Smaller: 1/22 (5) - Larger: 0/22 (0)	0/43 (0)	IVH: 1/43 (2) - Smaller: 1/21 (5) - Larger: 0/22 (0) PVL: 0/43 (0)	Fetal distress: 10/22 Preeclampsia: 1/22 Spontaneous: 5/22 Elective: 6/22	*Variety of postnatal cerebral imaging: both cUS and MRI.*

TABLE 4 (Continued)

First author, year	Patients	Definition sFGR	GA at birth in weeks	IUD	Neonatal mortality	Severe cerebral injury	Delivery indication	Comments
Batsry, 2020	*n* = 12	EFW of one twin <10th centile or intertwin EFW discordance ≥25% in the absence of TTTS or TAPS	32.0 (31.3–32.6)†	5/24 (23) - Smaller: 3/12 (25) - Larger: 2/12 (17) - Double: 2/12 (17)	0/19 (0)	Severe brain lesions on fetal MRI: 0/18 (0)	-	*Severe brain lesions were defined as IVH Grade III/IV, PVL or intraparenchymal hemorrhage.*
Couck, 2020	*n* = 26	EFW <3rd centile in one twin or at least two of the following: - EFW of one twin <10th centile, - AC of one twin <10th centile, - EFW discordance ≥25%, - UA PI of the smaller twin >95th centile	32.0 (29.4–32.4)†	0/52 (0)[a]	3/52 (6)[a] - Smaller: 2/26 (8) - Larger: 1/26 (4)	-	-	*Seven pregnancies underwent intervention (5 CO, 1 RFA, 1 TOP) and these were included in the analysis of GA at birth, but not in the analysis of the secondary outcomes.*
Shinar, 2021	*n* = 328	EFW of one twin <10th centile and intertwin EFW discordance ≥25%	31.8 (±3.6)‡	51/638 (8) - Smaller: 35/310 (11) - Larger: 16/328 (5) - Double: 16/328 (5)	18/587 (3) - Smaller: 14/275 (5) - Larger: 4/312 (1)	Neonatal cUS: IVH ≥ grade II:12/532 (2) - Smaller: 3/246 (1) - Larger: 9/286 (3) PVL: 7/532 (1) - Smaller: 4/246 (2) - Larger: 3/286 (1)	Fetal distress: 106/308 Maternal distress: 20/308 IUD/abnormal biophysical profile: 36/308 Spontaneous: 46/308 Elective: 100/308	*Grade of PVL not reported.*
Aquino, 2021	*n* = 3	EFW <3rd centile in one twin or at least two of the following: - EFW of one twin <10th centile, - AC of one twin <10th centile, - EFW discordance ≥25%, - UA PI of the smaller twin >95th centile	28.3 (±2.3)‡	0/6 (0)	1/6 (17) - Smaller: 0/3 (0) - Larger: 1/3 (33)	Severe cerebral injury on neonatal cUS: 0/6 (0)	-	*Severe cerebral injury was defined as IVH grade III/IV, PVL grade II/III or porencephalic cysts.*

Note: Data are presented as median (interquartile range)†, mean (± standard deviation)‡, mean (min-max)§ or *n*/N (%).

Abbreviations: AC, abdominal circumference; BCC, bipolar cord coagulation; BW, birthweight; CO, cord occlusion; cUS, cerebral ultrasound; EFW, estimated fetal weight; GA, gestational age; IUD, intrauterine demise; IVH, intraventricular hemorrhage; MRI, magnetic resonance imaging; PI, pulsality index; PVL, periventricular leukomalacia; RFA, radiofrequency ablation; sFGR, selective fetal growth restriction; TAPS, twin anemia polycythemia sequence; TOP, termination of pregnancy; TTTS, twin to twin transfusion syndrome; UA, umbilical artery.

[a]Authors have been approached for additional data.

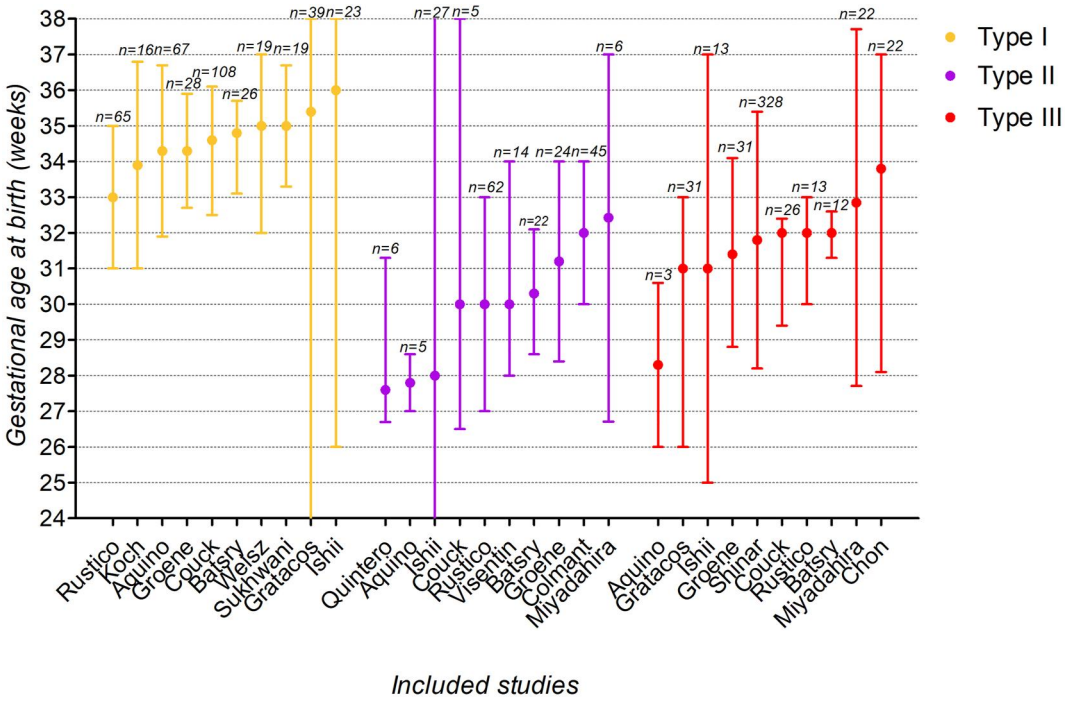

FIGURE 2 GA at birth per included study in twin pregnancies complicated by selective fetal growth restriction type I, II and III twins. This figure should be interpreted with care due to the heterogeneity of available studies, reporting gestational age at birth in either mean or median, using different definitions of outcomes measures and having small sample sizes

was delivered due to fetal deterioration (4/23), growth arrest smaller twin (3/23) or spontaneous labor/maternal indication (20/23).[11]

3.2.2 | Perinatal mortality

sFGR type I twins had an IUD rate between 0% and 4% and neonatal mortality rate between 0% and 10%. No perinatal mortality occurred in the cohorts of Weisz et al. ($n = 19$), Koch et al. ($n = 16$), Batsry et al. ($n = 26$) and Sukhwani et al. ($n = 19$).[12,15,19,22] The lowest neonatal mortality rate was reported in the study with the highest GA at birth (Ishii et al.[11]). In addition, the study with the highest perinatal mortality rate [Rustico et al. ($n = 65$) with 4% (5/130) IUD and 10% (12/118) neonatal mortality[14]] had the lowest GA at birth. However, this cohort included three bipolar cord coagulations following a change in the Doppler pattern to type II, one termination of pregnancy and one miscarriage. Nearly all studies reported that the smaller twin was the one affected by perinatal death, except for Gratacós et al. ($n = 39$), Ishii et al. ($n = 23$) and Couck et al. ($n = 108$) in which the IUD rate was similar for the larger and smaller twin in type I cases (double IUDs except for Ishii et al.).[4,11,23]

3.2.3 | Cerebral injury

Only 7/10 studies reported on cerebral injury, which was only observed in 2% of the cohort of Ishii et al. (1/44) and affected the smaller twin.[11]

3.3 | sFGR type II

Ten cohort studies assessing the GA at birth in sFGR type II were included with the number of pregnancies per cohort ranging from 5 to 62 (Table 3).

3.3.1 | GA at birth

sFGR type II cases were born at a GA at birth between 27.6 and 32.4 weeks. The lowest GA at birth was reported by Quintero et al. ($n = 6$), with a median GA at birth of 27.6 (26.7–31.3) weeks.[18] Miyadahira et al. ($n = 6$) reported the highest median GA at birth of 32.4 (26.7–37.0) weeks.[16] Only 4/10 studies described indication of delivery. The majority of the sFGR type II/III cohort (individual indications not reported) of Miyadahira et al. was delivered due to fetal distress (19/27), and others due to threatened preterm labor (2/27), IUD (4/27) or spontaneous labor ≥34 weeks (2/27). The cohort of Quintero et al. were all delivered due to fetal indications: A/REDF (2/6), non-reassuring fetal testing (3/6) and preterm premature rupture of membranes (1/6). The main reasons for delivery in the cohort of Ishii et al. were fetal deterioration (9/27), spontaneous labor/maternal indication (8/27), double IUD (4/27), growth arrest smaller twin (3/27) and miscarriage (2/27).[11] The cohort of Visentin et al. ($n = 14$) was delivered at a median GA at birth of 30 (28–34) weeks either following signs of fetal demise, an abnormal biophysical fetal profile or fetal indications including abnormal cardiotocography or absent or reversed a-wave in ductus venosus.[13]

3.3.2 | Perinatal mortality

sFGR type II twins demonstrated a relatively high IUD rate between 0% and 40% and neonatal mortality rate between 0% and 38%. The cohorts of Visentin et al. (n = 14) and Aquino et al. (n = 5) were the only two cohorts in which perinatal mortality did not occur, despite the relatively low GA at birth reported by the latter.[13,25] The absence of IUD in the cohort of Aquino et al. could be explained by the late inclusion of pregnancies (median GA at diagnosis = 24.8 weeks). Interestingly, the highest perinatal mortality occurred in the cohort born at a median GA at birth of 30.0 (26.5–38.0) weeks, namely Couck et al. (n = 5), who reported an IUD rate of 40% (4/10) and no neonatal mortality.[23] Additionally, the lowest IUD rate was reported in the cohort of Quintero et al. (n = 6) delivered at the lowest GA at birth.[18] These results, as well as the results described by Aquino et al. (n = 5), can be substantially impacted by their small sample size. Furthermore, almost all studies reported higher perinatal mortality in the smaller twin, except for the cohort of Batsry et al. (n = 22) and Couck et al. (n = 5) in which the IUD rate was similar for the larger and smaller twin (double IUDs).[22,23]

3.3.3 | Cerebral injury

sFGR type II cases had the highest rates of cerebral injury (between 2% and 30%) of all three types which was documented in 7/10 studies. The lowest severe cerebral injury rate [2% (1/43)] occurred in the type II cohort of Groene et al. (n = 24).[17] The highest severe cerebral injury rate of 30% (3/10) was reported in the cohort of Quintero et al. delivered at the lowest GA at birth.[18] Furthermore, in Ishii et al. (n = 27), Batsry et al. (n = 22) and Aquino et al. (n = 5) the smaller twin presented with more severe cerebral injury than the larger twin, while Miyadahira et al. (n = 6), Groene et al. (n = 24) and Quintero et al. (n = 6) reported the opposite.

3.4 | sFGR type III

Ten cohort studies assessing the GA at birth in sFGR type III were included, with the number of pregnancies ranging from 3 to 328 (Table 4).

3.4.1 | GA at birth

sFGR type III cases were born at a GA at birth between 28.3 and 33.8 weeks. The lowest GA at birth was presented in the type III cohort of Aquino et al. (n = 3), with a mean GA at birth of 28.3 (±2.3) weeks.[25] The highest median GA at birth of 33.8 (28.1–37.0) weeks was described by Chon et al.[20] Only four studies reported on the indication of delivery. The majority of the cohort of Ishii et al. was delivered due to fetal deterioration (8/13), while others either due to growth arrest of smaller twin (1/13) or spontaneous labor/maternal indication (4/13).[11] The cohort of Chon et al. (n = 22) was delivered either due to non-reassuring fetal status (10/22), spontaneous delivery (5/22), elective delivery (6/22) or preeclampsia (1/22). Miyadahira et al. (n = 22) reported on the indication of delivery for both type II/III combined as previously described.[16] The main reasons for delivery in the cohort of Shinar et al. (n = 328) with a mean GA at birth of 31.8 (±3.6) weeks, were fetal distress including abnormal cardiotocography or absent or reversed a-wave in ductus venosus (106/308), maternal diabetes (20/308), IUD/abnormal biophysical profile (36/308), spontaneous labor (46/308) and elective birth (100/308).[24]

3.4.2 | Perinatal mortality

sFGR type III twins had an IUD rate between 0% and 23% and neonatal mortality rate between 0% and 17%. The cohorts of Couck et al. (n = 26) and Aquino et al. (n = 3) were the only two cohorts in which IUD did not occur.[23,25] Neonatal mortality was absent in the cohorts described by Chon et al. (n = 22), who described the most advanced GA at birth, and Batsry et al. (n = 12) who reported the highest IUD rate of 23% (5/24) in a cohort born at a median GA of 32.0 (31.3–32.6) weeks.[20,22] The highest neonatal mortality rate of 17% (1/6) were reported by Aquino et al. (n = 3), who also reported the lowest GA at birth.[25] The majority of studies conclude that the smaller twin more often presented with perinatal mortality than the larger twin, except Groene et al. (n = 31) in which the IUD rate was similar for the smaller and larger twin but the larger twin presented with higher risk of neonatal mortality, and Ishii et al. (n = 13) and Aquino et al. (n = 3) in which the larger twin also presented with a higher neonatal mortality rate.[11,17,25]

TABLE 5 Summarized perinatal outcome ranges of MC twin pregnancies complicated by sFGR according to Gratacós type

	sFGR type I	sFGR type II	sFGR type III
GA at birth	33.0–36.0 weeks	27.6–32.4 weeks	28.3–33.8 weeks
Intrauterine demise	0%–4%	0%–40%	0%–23%
Neonatal mortality	0%–10%	0%–38%	0%–17%
Cerebral injury	0%–2%	2%–30%	0%–33%

Note: These numbers should be interpreted with care due to the heterogeneity of available studies, reporting GA at birth in either mean or median, using different definitions of outcomes measures and having small sample sizes.

Abbreviations: GA, gestational age; MC, monochorionic; sFGR, selective fetal growth restriction.

3.4.3 | Cerebral injury

Cerebral injury in sFGR type III cases was documented in 8/10 studies and varied between 0% and 33%. Batsry et al. ($n = 12$) and Aquino et al. ($n = 3$) were the only cohorts in which severe cerebral injury did not occur.[22,25] The highest severe cerebral injury rate of 33% (8/24) occurred in the cohort of Ishii et al. ($n = 13$), which was born at a median GA of 31 (25–37) weeks.[11] Interestingly, Ishii et al. ($n = 13$), Gratacós et al. ($n = 31$) and Groene et al. ($n = 31$) reported a higher severe cerebral injury rate in the larger twin, while Miyadahira et al. ($n = 22$) and Chon et al. ($n = 22$) identified the smaller twin to be at higher risk.

4 | SUMMARY

The summarized findings per sFGR type are presented in Table 5. Overall, sFGR type I showed the most favorable outcomes, with GA at birth ranging from 33.0 to 36.0 weeks, a perinatal mortality rate (IUD and neonatal mortality combined) between 0% and 10% and 0%–2% cerebral injury. sFGR type II presented with the poorest outcomes, with a GA at birth between 27.6 and 32.4 weeks, a perinatal mortality rate ranging between 0% and 40% and a cerebral injury rate of 2%–30%. sFGR type III is reported to have relatively similar outcomes as type II, albeit slightly better, with a GA ranging from 28.3 to 33.8 weeks, a perinatal mortality rate of 0%–23% and cerebral injury in 0%–33%.

5 | DISCUSSION

5.1 | Summary of the key findings

This systematic review shows that sFGR type I twins are generally born at a later GA than type II and type III twins and have a lower rate of IUD, neonatal mortality and cerebral injury. Nearly all studies reported that the smaller twin was especially at a disadvantage for adverse perinatal outcomes. However, the reported GA at birth of MC twins complicated by sFGR varies substantially between studies as well as the incidence of IUD, neonatal mortality and cerebral injury, especially in sFGR type II and III cohorts. Importantly, the 17 included studies had heterogenous study populations with different definitions of sFGR and timing of inclusion (between the first and third trimester), and reported on different perinatal outcome measures. Hence, this systematic review primarily demonstrates the knowledge gap regarding the optimal GA at birth and the lack of uniform outcome measures (assessment and management of expectantly managed MC twins complicated by sFGR and the lack of uniformity in various definitions). The application of the Gratacós classification substantially differs between studies, hampering proper comparison of outcomes between the types of sFGR.

5.2 | Strengths and limitations

Five main recurring limitations can be identified in current literature: (1) information bias due to retrospective study designs, (2) small sample sizes, (3) the use of different antenatal management protocols (including frequency and methods of fetal surveillance) and definitions of sFGR, (4) lack of detailed information on perinatal outcomes categorized per Gratacós type, (5) lack of standardized neonatal and long-term follow-up including uniform definitions of perinatal outcome measures. Additionally, we did not synthesize our data in the form of a meta-analysis. Therefore, evidence of the association between GA at birth and adverse neonatal outcomes in MC twins with sFGR is considered to be of low quality. However, our review provides an elaborate and most recent overview of GA at birth in sFGR twins, demonstrating great variation between centers and emphasizing the uncertainty regarding the optimal timing of delivery after expectant management.

5.3 | Interpretation of the findings

Our review demonstrates that type II and type III sFGR twins are generally born at a lower GA and have an increased rate of perinatal and neonatal mortality and severe cerebral injury as opposed to type I. However, we also demonstrate the current lack of knowledge on the average GA at birth for the different types of sFGR due to limitations in the available literature leading to incomparability between studies.

A crucial limitation that is persistently present in current literature is the different scoring methods used for the Gratacós classification. Its dynamic nature hampers the determination of a "definitive" Gratacós type. At present, available studies base the classification of a pregnancy complicated by sFGR on either a single observation of abnormal UA Doppler flow patterns, the final UA Doppler flow pattern prior to delivery or the most prevalent Doppler flow pattern.[17,24,26] Therefore, the classification of sFGR according to Gratacós is still not uniformly applied in literature, leading to substantial incomparability between studies with regards to outcome per sFGR type. It was recently suggested that a modification of the Gratacós classification is necessary that includes GA at diagnosis, variation in UA Doppler flow patterns, ductus venosus Doppler (has been shown to be a powerful prognostic marker for sFGR and might identify infants with increased risk for neonatal mortality and morbidity[27]) and the co-existence of TTTS.[28] By reaching an international consensus on an update of the current classification system, outcome parameters can be properly compared between studies and antenatal prognostication can be further improved.

A previous systematic review and meta-analysis by Townsend et al. also explored the perinatal outcomes of sFGR categorized according to the Gratacós classification.[29] A noteworthy difference between our two studies is the significantly higher cerebral injury rates after expectant management in type II and type III reported by

Townsend et al. This can be the consequence of improved care over the years, as Townsend et al. primarily included older studies (2001–2017), while our review included more recent studies (2007–2021). Yet, accurate comparison of our studies is hampered by different aims and methods. While we focused on the international variation in GA at birth and perinatal outcome in this systematic literature review, Townsend et al. investigated the impact of different management strategies on perinatal outcomes in a meta-analysis. Interestingly, a similar outcome will be investigated by the FERN study with the aim to determine whether it is feasible to conduct a randomized control trial of active intervention versus expectant management.[30]

Buca et al. showed similar results in their systematic review and meta-analysis exploring the outcomes of sFGR according to UA Doppler pattern of the smaller twin[31] sFGR type I twins were also born at a significantly higher GA compared to type II [Median difference: 2.8 (95% CI, 1.83–3.86) weeks] and type III [Median difference: 2.1 (95% CI, 0.97–3.19) weeks]. This meta-analysis showed a significantly higher risk of perinatal mortality [OR, 4.1 (95% CI, 1.6–10.3)] and abnormal postnatal brain imaging in sFGR type II and III compared to Type I [Type II: OR, 4.9 (95% CI, 1.9–12.9), Type III: OR, 8.2 (95% CI, 2.0–33.1)]. Noteworthy, Buca et al. excluded studies reporting only one type of sFGR and included 13 studies (2007–2017), while our systematic review included 17 more recently published studies (2007–2021) with minimal overlap.

A third study following from the retrospective multicenter cohort study by Shinar et al. (of which data is also included in this review), focusing on outcomes of type III pregnancies, showed a GA dependent decrease in neonatal morbidity in sFGR type III with low rates of neurological morbidity.[24] Remarkably, a large decline in risk was seen from 29 weeks' gestation (74%) to 30 weeks (45%). It should be noted that postnatal brain ultrasound examinations were only routinely performed for neonates delivered before 32 weeks, resulting in a potential underestimation of brain injury. In addition, the study did not take into account the possibility of cases changing Gratacós types during pregnancy, resulting in a potential misclassification (especially in type II/III).

The findings from the study by Shinar et al. and our review are in agreement with the systematic review by Inklaar et al., which showed a significantly increased risk of cerebral injury in cohorts with a lower GA at birth.[32] Inklaar et al. illustrated that the odds of cerebral injury decreased with a factor of 0.65 for each additional increase in week of GA at birth. The increased risk of cerebral injury was thought to be primarily associated with a lower GA at birth, but could also be due to an indicated urgent caesarean section in more severe cases. The review by Inklaar et al., however, lacks a distinction between Gratacós types and also reports high heterogeneity between the studies and small sample sizes, which are similar limitations as were found in this systematic review.

Based on our systematic literature review and the previously mentioned review by Inklaar et al., it can be concluded that sFGR type II and type III are especially at increased risk of cerebral injury. The cause of this injury is unknown, and could be related to in utero adverse environment with abnormal flows and/or it could be a consequence of (iatrogenic) prematurity. In order to determine the timing of cerebral injury, routine and repeated neuroimaging examinations should be performed during fetal and neonatal life. The presence of cerebral injury already in utero or directly after birth would point towards a causal relation with adverse in utero environment, whereas cerebral injury which becomes apparent only 1/2 weeks after birth would point towards a causal relation with (iatrogenic) prematurity. Importantly, both prematurity and neonatal cerebral injury are associated with an increased risk of long-term neurodevelopmental impairment. The risk for developmental delay is known to increase exponentially with decreasing GA (OR per week' gestation: 1.13, 95% CI 1.08–1.18).[33–35] Furthermore, the IQ of children delivered <34 weeks' gestation decreases by 2.34 (95% CI: −2.99, −1.70) points with each lower GA week.[36]

5.4 | Clinical and research implications

In conclusion, due to the high heterogeneity of published studies, uncertainty regarding the optimal GA at birth in MC twins complicated by sFGR persists. Our review emphasizes the uncertainty regarding the optimal timing of delivery after expectant management. Additionally, it demonstrates the varying GA at birth, rates of IUD and adverse neonatal outcome between international centers in sFGR twins, stratified according to sFGR classification. In order to estimate the optimal timing of delivery, future prospective studies should implement uniform diagnostic criteria for sFGR itself and the Gratacós classification, and objective and uniform management protocols with standardized perinatal outcome measures reported according to Gratacós type prior to delivery.[37] Indication for delivery should be included as well as a description of neonatal morbidity. International collaboration is warranted to increase sample size. In addition, standardized long-term follow-up should be included to assess the effect of perinatal management and timing of delivery on long-term outcome.[38] Subsequently, a meta-analysis can be performed categorizing perinatal outcome measures according to GA at birth. In the absence of a randomized controlled trial, larger and standardized data from retrospective and prospective studies can help us elucidate the optimal timing of delivery for MC twins with sFGR and ensure a more favorable perinatal outcome for these vulnerable neonates.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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APPENDIX

Search strategy

PubMed

("Fetal Growth Retardation"[Mesh] OR "Fetal Growth Retardation"[TW] OR "Fetal Growth Restriction"[TW] OR "Foetal Growth Retardation"[TW] OR "Foetal Growth Restriction"[TW] OR "Intrauterine Growth Restriction"[TW] OR "Intrauterine Growth Retardation"[TW] OR "SIUGR"[TW] OR "IUGR"[TW]) AND ("Twins, Monozygotic"[Mesh] OR "Monozygotic Twin"[TW] OR "Monozygotic Twins"[TW] OR "Identical Twin"[TW] OR "Identical Twins"[TW] OR "Monochorionic Diamniotic"[TW] OR "Monochorionic"[TW]) AND ("Gestational Age"[Mesh] OR "Gestational Age"[TW] OR "Gestational Ages"[TW] OR "Fetal Age"[TW] OR "Fetal Ages"[TW] OR "Foetal Age" OR "Foetal Ages") AND ("2007"[Date -- Publication]: "3000"[Date – Publication])

Results 09-06-2022: 213

EMBASE

(exp intrauterine growth retardation/ OR "Fetal Growth Retardation".ti,ab. OR "Fetal Growth Restriction".ti,ab. OR "Foetal Growth Retardation".ti,ab. OR "Foetal Growth Restriction".ti,ab. OR "Intrauterine Growth Restriction".ti,ab. OR "Intrauterine Growth Retardation".ti,ab. OR "SIUGR".ti,ab. OR "IUGR".ti,ab.) AND (exp monozygotic twins/ OR "Monozygotic Twin".ti,ab. OR "Monozygotic Twins".ti,ab. OR "Identical Twin".ti,ab. OR "Identical Twins".ti,ab. OR "Monochorionic Diamniotic".ti,ab. OR "Monochorionic".ti,ab.) AND (exp gestational age/ OR "Gestational Age".ti,ab. OR "Gestational Ages".ti,ab. OR "Fetal Age".ti,ab. OR "Fetal Ages".ti,ab. OR "Foetal Age".ti,ab. OR "Foetal Ages".ti,ab.) NOT (conference OR conference abstract OR "conference review").pt. AND 2007:2023. (sa_year).

Results 09-06-2022: 338

Web of science

TS=("Fetal Growth Retardation" OR "Fetal Growth Restriction" OR "Foetal Growth Retardation" OR "Foetal Growth Restriction" OR "Intrauterine Growth Restriction" OR "Intrauterine Growth Retardation" OR "SIUGR" OR "IUGR") AND TS=("Monozygotic Twin" OR "Monozygotic Twins" OR "Identical Twin" OR "Identical Twins" OR "Monochorionic Diamniotic" OR "Monochorionic") AND TS=("Gestational Age" OR "Gestational Ages" OR "Fetal Age" OR "Fetal Ages" OR "Foetal Age" OR "Foetal Ages") AND PY=(2007–2023)

Results 09-06-2022: 162

Cochrane

("Fetal Growth Retardation" OR "Fetal Growth Restriction" OR "Foetal Growth Retardation" OR "Foetal Growth Restriction" OR "Intrauterine Growth Restriction" OR "Intrauterine Growth Retardation" OR "SIUGR" OR "IUGR"):ti,ab,kw AND ("Monozygotic Twin" OR "Monozygotic Twins" OR "Identical Twin" OR "Identical Twins" OR "Monochorionic Diamniotic" OR "Monochorionic"):ti,ab,kw AND ("Gestational Age" OR "Gestational Ages" OR "Fetal Age" OR "Fetal Ages" OR "Foetal Age" OR "Foetal Ages"):ti,ab,kw

Results 09-06-2022: 10