



**HAL**  
open science

## Selective intrauterine growth restriction of monochorionic diamniotic twin pregnancies: What is the neonatal prognosis?

Letizia Gremillet, Antoine Netter, Barthélémy Tosello, Claude d'Ercole, Florence Bretelle, Cécile Chau

### ► To cite this version:

Letizia Gremillet, Antoine Netter, Barthélémy Tosello, Claude d'Ercole, Florence Bretelle, et al.. Selective intrauterine growth restriction of monochorionic diamniotic twin pregnancies: What is the neonatal prognosis?. *Journal of Gynecology Obstetrics and Human Reproduction*, 2022, 51 (3), pp.102304. 10.1016/j.jogoh.2021.102304 . hal-03828889

**HAL Id: hal-03828889**

<https://hal.science/hal-03828889v1>

Submitted on 6 Apr 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Selective intrauterine growth restriction of monochorionic diamniotic twin pregnancies: What is the neonatal prognosis?

Letizia Gremillet<sup>a,\*</sup>, Antoine Netter<sup>a,b,\*</sup>, Barthélemy Tosello<sup>c,d</sup>, Claude D'Ercole<sup>a,e</sup>, Florence Bretelle<sup>a,f</sup>, Cécile Chau<sup>a</sup>

<sup>a</sup> Department of Gynecology and Obstetrics, AP-HM, Assistance Publique-Hôpitaux de Marseille, Marseille, France

<sup>b</sup> Aix Marseille Univ, Avignon University, CNRS, IRD, IMBE, Marseille, France

<sup>c</sup> Department of Neonatal Medicine, North Hospital, Assistance Publique-Hôpitaux de Marseille, Marseille, France

<sup>d</sup> CNRS, EFS, ADES, Aix-Marseille Univ, Marseille, France

<sup>e</sup> EA3279, CEReSS, Health Service Research and Quality of Life Center, Aix-Marseille University, 13284, Marseille, France

<sup>f</sup> Research Unit on Tropical and Emerging Infectious Diseases, UM63, CNRS 7278, IRD 198, INSERM 1095, Marseille, France

---

## A B S T R A C T

**Objective:** This study compares the neonatal morbidity and mortality of the smallest twins of monochorionic diamniotic (MCDA) pregnancies complicated with selective intrauterine growth restriction (sIUGR) with newborns from singleton pregnancies with intrauterine growth restriction (IUGR).

**Methods:** We conducted a retrospective cohort study of patients managed at the prenatal diagnosis center in a single tertiary care hospital between 2012 and 2019. MCDA twin pregnancies complicated with sIUGR (sIUGR group) were compared with singleton pregnancies with IUGR (IUGR group). The primary outcome was the comparison in neonatal morbidity and mortality between the two groups.

**Results:** The analysis included 251 patients: 67 in the sIUGR group and 184 in the IUGR group. The two groups were comparable in gestational age and birth weight ( $p > 0.05$ ). Multivariate analysis controlling for factors that may influence neonatal status showed no significant difference between the two groups in any of the neonatal morbidity criteria or the composite morbidity-mortality endpoint (adjusted OR = 0.946 [95% CI = 0.317–2.827];  $p = 0.921$ ).

**Conclusion:** Despite supposedly different pathophysiological mechanisms, neonates from MCDA pregnancies complicated with sIUGR and those from singleton pregnancies with IUGR appear to have identical neonatal morbidity and mortality.

### Keywords:

Monochorionic twin pregnancies; Intrauterine growth restriction  
Neonatal morbidity

---

## Introduction

Selective intrauterine growth restriction (sIUGR) is a fetal pathology that affects between 10% and 15% of monochorionic diamniotic (MCDA) twin pregnancies [1].

Intrauterine growth restriction (IUGR), which can affect singleton pregnancies, and sIUGR are two distinct fetal pathologies that share obvious similarities, particularly in their definitions, which are essentially based on fetal growth that is considered insufficient for gestational age [2,3]. These similarities have led to the formulation of identical names under the term “growth restriction” which further reinforces the assimilation of these two ultrasound situations. This assimilation has probably dictated clinical attitudes that are similar from one pathology to the other. In fact, the monitoring and

indications for births are almost identical and essentially based on the analysis of Doppler, growth, and fetal heart rate [1,4,5]. However, the two pathologies involve different pathophysiological mechanisms. Placental insufficiency, defined as decreased maternal-placental blood flow and oxygen supply, is the primary cause of IUGR [6,7]. Inadequate trophoblastic invasion, impaired fetoplacental perfusion, remodeling of the normal placental vasculature, and reduced placental development are implicated [7–12]. In comparison, the pathophysiological mechanisms involved in the constitution of a sIUGR are the inequitable sharing of the placenta and the presence of vascular anastomoses, particularly arterio-arterial [13–17]. While the consequences in terms of obstetrical prognosis and neonatal and infant morbidity have been well studied and are known for IUGR, they remain largely unknown for sIUGR [18]. The risk of intrauterine fetal death (IUFD) or cerebral lesions in sIUGR is related to the umbilical end-diastolic flow according to the Gratacós classification [19,20]. Data on neonatal outcomes for live-born infants is scarce and has

only been reported in a small number of mostly retrospective and small-scale studies [21].

We conducted this study to compare the morbidity and mortality of the smallest twins of MCDA pregnancies with sIUGR and newborns from singleton pregnancies with IUGR.

## Materials and methods

### Study design

We conducted a retrospective cohort study of patients managed between January 2012 and December 2019 at the prenatal diagnosis center of the North Hospital in Marseille (France), a referral hospital for the management of MCDA pregnancies. The study was approved by the ethics committee of the University of Aix-Marseille.

### Study population

Two groups of patients were eligible for the study: (1) patients followed in our department for an MCDA pregnancy with sIUGR and (2) patients followed for a singleton pregnancy with IUGR. Concerning the sIUGR group, the inclusion criteria were a twin MCDA pregnancy which monochorionicity as well as due date had been affirmed by an ultrasound scan in the first trimester; an estimated fetal weight (EFW) by the Hadlock formula [22] lower than the third percentile on one of the fetuses, or two or more of the following parameters combined: (i) EFW below the 10th percentile, (ii) abdominal circumference below the 10th percentile, (iii) growth discordance greater than or equal to 25% between the two twins, and (iv) an umbilical artery pulsatility index of the affected twin above the 95th percentile [23]; and delivery after 24 gestational weeks (GW). The exclusion criteria were the presence of a chromosomal, genetic, malformative, or infectious etiology suspected and/or found during the etiological work-up; the IUFD of one or both twins; pregnancies complicated by twin-to-twin transfusion syndrome (TTTS) according to the diagnostic criteria of Quintero [24] or the twin anemia-polycythemia sequence (MCA Doppler > 1.50 MoM in the donor and < 0.80 MoM in the recipient [25]); or any pregnancy that required a therapeutic fetal medicine procedure. The neonatal data for the sIUGR group refers to the smallest twin from an MCDA pregnancy with sIUGR. For the IUGR group, the inclusion criteria were definite dating by ultrasound in the first trimester; an isolated EFW below the third percentile on appropriate curves (for weight, height, maternal parity, and fetal sex) or an EFW below the 10th percentile according to these same curves, associated with a cessation of growth or inflection of growth [5,26,27]; and delivery after 24 GW. The exclusion criteria were the presence of a chromosomal, genetic, malformative or infectious etiology suspected and/or found during the etiological work-up; the occurrence of an IUFD; or the decision to medically terminate the pregnancy.

### Patient follow-up and neonatal management

All patients included in the study were followed since diagnosis and delivered in the obstetrics department of the Hôpital Nord (Marseille, France). Neonatal management was provided in the neonatology department of the Hôpital Nord. The main modalities of obstetrical management, which was performed according to the recommendations of the Collège National de Gynécologues Obstétriciens Français, remained unchanged throughout the study period and were similar for both groups [28]: bimonthly ultrasound monitoring of growth, weekly ultrasound monitoring of amniotic fluid quantity, and Doppler of the umbilical artery, middle cerebral artery, and ductus venosus. Monitoring by a midwife at home was performed when the diagnosis of IUGR was made. Hospitalization was indicated for absent umbilical artery end-diastolic flow. The criteria for fetal

extraction were (1) before 32 GW: absent or reversed Doppler A wave at the ductus venosus and/or recurrent fetal heart rhythm abnormalities; (2) between 32 and 34 GW: absent or reverse umbilical artery end-diastolic flow; (3) between 34 and 37 GW: growth arrest; or (4) extraction at 37 GW or at the time of diagnosis after 37 GW.

The use of laser photocoagulation of placental vascular anastomoses was reserved in our center for MCDA pregnancies complicated with TTTS. MCDA pregnancies complicated with isolated sIUGR without TTTS (patients in the sIUGR group) were not treated in this way.

### Endpoints

The primary outcome was the difference in neonatal morbidity and mortality between the smallest twins of MCDA pregnancies with sIUGR and newborns from singleton pregnancies with IUGR. We defined a neonatal morbidity endpoint including the occurrence of one or more of the following: (i) grade 3–4 intraventricular hemorrhage, (ii) stage II or III periventricular cystic leukomalacia [29], (iii) necrotizing enterocolitis of stage 3 or higher [30], and (iv) severe bronchopulmonary dysplasia, defined as requiring oxygen for at least 28 days in addition to the need for 30% oxygen or more and/or mechanical respiratory support or continuous positive airway pressure at 36 weeks of amenorrhea [31]. We defined the composite endpoint of severity to include the occurrence of neonatal morbidity or neonatal death.

The secondary endpoints were comparison of neonatal mortality, independent neonatal morbidity criteria (umbilical pH at birth, Apgar score, rate of acute respiratory distress, duration of ventilatory support, brain abnormality on MRI, ulcerative enterocolitis, sepsis, rate of admission to intensive care). Obstetric birth characteristics were also compared between the two groups (cesarean section rate, birth indications, gestational age at birth, birth weight, time from diagnosis to birth).

### Statistical analysis

The sample size was constrained by the time period defined for the study, which was the earliest date that patient records could be accessed by computer in our center.

Data is reported using means  $\pm$  standard deviations or medians (minimum - maximum) for quantitative variables and using counts (percentages) for categorical variables.

First, population characteristics, obstetric delivery characteristics, and neonatal morbidity and mortality criteria were compared between the two groups. The Student *t*-test (or Mann–Whitney *U* test when necessary) was used to compare quantitative variables. The normality of the distribution of quantitative variables was previously checked by Levene's test. Categorical variables were compared using the chi-square test.

Second, to compare neonatal outcomes independently of differences between the two groups, multivariate analysis was performed with statistical adjustment for gestational age at birth, birth weight, fetal sex, indication for birth (divided into five categories: spontaneous, fetal heart rhythm abnormalities, fetal Doppler abnormalities, fetal growth arrest, and other causes), and severity of Doppler abnormalities before birth (intermittent, permanent, or positive null umbilical end diastolic flow). Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs).

All tests were two tailed, and results were considered significant if the *p* value obtained was less than 0.050. These analyses were performed using IBM SPSS Statistics software version 20.0 (IBM Inc., New York, USA).

## Results

### Population and pregnancy characteristics

Between January 2012 and December 2019, 184 patients were followed for sIUGR at our center; 17 patients were not included because an etiology other than vascular, 100 patients were excluded from the analysis because of the occurrence of TTTS ( $n = 18$ ) and/or IUFD ( $n = 90$ ) of at least one of the two twins. Sixty-seven patients were thus included in the sIUGR group. Two hundred and sixty-four patients were followed for IUGR; 63 patients were not included because an etiology other than vascular was identified and 17 patients because an IUFD occurred. One hundred and eighty-four patients were thus included in the IUGR group. The demographic characteristics of the patients and data related to the course of the pregnancy are presented in Table 1. The mean age of the patients was comparable between the sIUGR and IUGR groups ( $29.7 \pm 5.4$  and  $30.0 \pm 6.2$  years, respectively;  $p = 0.671$ ) as well as the median parity

**Table 1**

Comparison of demographic and pregnancy characteristics between the 'selective intrauterine growth retardation' and 'intrauterine growth retardation' groups.

	N	sIUGR	IUGR	P-value
Number of patients, n		67	184	
Age, years, mean $\pm$ SD	251	$29.7 \pm 5.4$	$30.0 \pm 6.2$	0.671
Gravidity, n, median (min-max)	251	2 (1 – 10)	2 (1 – 11)	0.896
Parity, n, median (min-max)	251	0 (0 – 5)	0 (0 – 10)	0.814
BMI, kg/m <sup>2</sup> , mean $\pm$ SD	251	$24.5 \pm 5.4$	$26.0 \pm 6.1$	0.081
Gestational age at diagnosis, Weeks, median (min-max)	251	25 (12 – 37)	26 (18 – 36)	0.077 <sup>a</sup>
Umbilical artery end-diastolic flow at the time of diagnosis,	251			0.003 <sup>**</sup>
Persistently positive		47/67 (70.1%)	158/184 (85.9%)	
Intermittently absent or intermittently reversed		11/67 (16.4%)	8/184 (4.3%)	
Persistently absent or persistently reversed		9/67 (13.4%)	18/184 (9.8%)	
Null or negative a-wave at Ductus Venosus		0/67 (0.0%)	1/184 (0.5%)	1.000 <sup>b</sup>
Growth discrepancy at diagnosis, %, mean $\pm$ SD		$22.4 \pm 7$	–	
Growth percentile at diagnosis, %, mean $\pm$ SD		–	$4.3 \pm 5.1$	
Fetal sex, n/N (%)	251			0.282
Male		39/67 (58.2%)	93/184 (50.5%)	
Female		28/67 (41.8%)	91/184 (49.5%)	
Antenatal corticosteroid therapy, n/N (%)	251			0.384
Not performed		23/67 (34.3%)	69/184 (37.5%)	
Incomplete		1/67 (1.5%)	9/184 (4.9%)	
Complete		43/67 (64.2%)	106/184 (57.6%)	

sIUGR: Selective IntraUterine Growth Retardation.

IUGR: IntraUterine Growth Retardation.

Continuous variables are compared by student's t-test. Categorical variables are compared by Pearson's Chi2 test. Results are presented as mean  $\pm$  standard deviation or medians (minimum-maximum) for continuous variables and count/total (%) for categorical variables.

<sup>a</sup> Mann-Whitney U test (non-parametric variables).

<sup>b</sup> Fisher's exact test (insufficient numbers to perform Pearson's Chi2 test).

<sup>c</sup> Length of stay in the ICU, excluding ICU deaths and newborns who were not admitted to the ICU.

<sup>d</sup> Length of hospital stay and duration of ventilatory support excluding deaths.

<sup>e</sup> Composite criterion including the occurrence of one or more of the following: (i) neonatal death, (ii) stage III or IV intraventricular hemorrhage, (iii) periventricular white matter cyst, (iv) bronchopulmonary dysplasia, (v) stage II or III ulcerative enterocolitis.

\*p-value < 0.05.

\*\* p-value < 0.01, \*\*\*p-value < 0.001

All statistical tests are two-sided.

(0 [0 – 5] and 0 [0 – 10];  $p = 0.814$ ). Gestational age at diagnosis was not different between the two groups (25 [12–37] and 26 [18–36] GW, respectively;  $p = 0.077$ ).

### Obstetrical data

Obstetric data for the deliveries is detailed in Table 2. cesarian section rates were comparable between the sIUGR (68.7%) and IUGR (73.9%;  $p = 0.409$ ) groups. Gestational age at birth was not different between the two groups (34 [25–38] and 33 [26–41] respectively;  $p = 0.984$ ), nor was birth weight ( $1545 \text{ g} \pm 567 \text{ g}$  and  $1475 \text{ g} \pm 670 \text{ g}$ , respectively;  $p = 0.448$ ). The median time from diagnosis to birth was not statistically different between the groups (8 [0 – 20] weeks vs. 6 [0 – 19] weeks, respectively;  $p = 0.068$ ). The frequency of distribution of the different events leading to birth was statistically different between the sIUGR and the IUGR groups: respectively, the rates were 41.8% versus 16.3% for spontaneous births; 26.9% versus 35.3% for births indicated due to fetal heart rate abnormalities; 13.4% versus 2.7% for fetal Doppler abnormalities; 13.4% versus 35.3% for fetal growth arrest; 3.0% versus 10.3% for preeclampsia; and 1.5% versus 0.0% for other causes ( $p < 0.001$ ). The last evaluation of the fetal umbilical artery end-diastolic flow before birth was statistically different between the two groups: positive in 52.2% of the fetuses of the sIUGR group versus 73.4% of the IUGR group; absent or reversed

**Table 2**

Comparison of demographic and pregnancy characteristics between the 'selective intrauterine growth retardation' and 'intrauterine growth retardation' groups.

	N	sIUGR	IUGR	P-value
Mode of delivery, n/N (%)				0.409
Vaginal	251	21/67 (31.3%)	48/184 (26.1%)	
Cesarean section		46/67 (68.7%)	136/184 (73.9%)	
Indication of birth, n/N (%)	251			<0.001 <sup>***</sup>
Spontaneous		28/67 (41.8%)	30/184 (16.3%)	<0.001 <sup>***</sup>
Fetal heart rate abnormality		18/67 (26.9%)	65/184 (35.3%)	0.207
Doppler abnormalities		9/67 (13.4%)	5/184 (2.7%)	0.001 <sup>**</sup>
Growth arrest		9/67 (13.4%)	65/184 (35.3%)	<0.001 <sup>***</sup>
Preeclampsia		2/67 (3.0%)	19/184 (10.3%)	0.063
Other		1/67 (1.5%)	0/184 (0.0%)	–
Gestational age at birth, Weeks, median (min-max)	251	34 (25 – 38)	33 (26 – 42)	0.984 <sup>a</sup>
Duration from diagnosis to birth, Weeks, median (min-max)	251	8 (0 – 20)	6 (0 – 19)	0.068 <sup>a</sup>
Umbilical artery end-diastolic flow before birth n/N (%)	251			0.001 <sup>**</sup>
Persistently positive		35/67 (52.2%)	135/184 (73.4%)	0.002 <sup>**</sup>
Intermittently absent or intermittently reversed		12/67 (17.9%)	29/184 (15.8%)	0.166
Persistently absent or persistently reversed		20/67 (29.9%)	20/184 (10.9%)	<0.001 <sup>***</sup>
Null or negative a-wave at Ductus Venosus before birth, n/N (%)	251	2/67 (3.0%)	1/184 (0.5%)	0.175 <sup>b</sup>
Birth weight, grams, mean $\pm$ SD	251	$1545 \pm 567$	$1475 \pm 670$	0.448
Growth discrepancy at birth, %, mean $\pm$ SD		$22.6 \pm 12.0$	–	–
Growth percentile at birth, %, mean $\pm$ SD		$2.2 \pm 2.4$	$1.7 \pm 2.2$	0.156 <sup>a</sup>

sIUGR: Selective IntraUterine Growth Retardation.

IUGR: IntraUterine Growth Retardation.

<sup>a</sup> Mann-Whitney U test (non-parametric variables).

<sup>b</sup> Fisher's exact test (insufficient numbers to perform Pearson's Chi2 test).

intermittently in 17.9% versus 15.8%, respectively; and absent or reversed permanently for 29.9% versus 10.9%, respectively ( $p = 0.001$ ). There was no significant difference between the two groups with respect to the null or negative  $a$ -wave at ductus venosus: 3.0% versus 0.5%, respectively ( $p = 0.175$ ).

### Neonatal data

Neonatal data between the two groups is presented in Table 3. Data for the sIUGR group refers to the sIUGR twin.

The composite endpoints of neonatal morbidity and mortality were not statistically different between the two groups: 20.9% for the sIUGR group and 25.0% for the IUGR group ( $p = 0.500$ ). The death rate was not statistically different between the groups (respectively, 9.0% vs. 6.0%;  $p = 0.406$ ). No significant differences were found for any of the other neonatal status endpoints: umbilical arterial pH at birth, Apgar score, rate of admission to intensive care, rate of respiratory distress, brain abnormalities on MRI, ulcerative enterocolitis, and sepsis ( $p \geq 0.050$  for all). Regarding the details of neonatal variables, only the bronchopulmonary dysplasia rate was statistically significant (4.5% vs. 14.1%, respectively;  $p = 0.034$ ).

The results of the multivariate analysis comparing the neonatal data are presented in Table 4. No statistically significant differences between the two groups were found after adjustment for the risk of occurrence of the composite endpoint of morbidity-mortality

(adjusted OR = 0.946 [95% CI = 0.317–2.827];  $p = 0.921$ ); mortality (adjusted OR = 0.210 [0.043–1.040];  $p = 0.056$ ); or any other neonatal variable (95% CI including 1.000 and  $p \geq 0.050$  for all).

Supplementary Table 1 describes the neonatal outcomes of the eutrophic twin. The mean birth weight was 1964 g  $\pm$  570 g; the mean pH was 7.31  $\pm$  0.07. The composite endpoint of morbidity and mortality was found in 16.4% of cases.

The results of the subgroup analysis determined by the last umbilical diastole before birth are presented in Supplementary Table 2. No statistically significant difference between the two groups was found regarding the composite endpoint nor any other neonatal variables ( $p \geq 0.050$  for all endpoints).

### Discussion

Our retrospective study compares obstetric and neonatal outcomes of fetuses with either sIUGR in the context of twin MCDA pregnancies or IUGR in singleton pregnancies. In compliance with our protocols derived from current recommendations, patients in both groups received very similar surveillance, and the criteria used to decide on the birth were essentially the same. The results of our study seem to suggest that the short-term prognosis of the newborns was similar for both groups. Indeed, no significant difference was found between the two groups for each of the criteria assessing neonatal morbidity and mortality. In particular, the occurrence of the

**Table 3**  
Comparison of neonatal status between the 'selective intrauterine growth restriction' and 'intrauterine growth restriction' groups.

	N	sIUGR	IUGR	P-value
APGAR score, median (min-max)				
	1 min	251	9 (2 – 10)	9 (0 – 10) 0.312
	5 min	251	10 (6 – 10)	10 (0 – 10) 0.892
	10 min	251	10 (2 – 10)	10 (0 – 10) 0.626
APGAR score < 7, n/N (%)				
	1 min		16/67 (23.9%)	59/184 (32.1%) 0.210
	5 min		8/67 (11.9%)	19/184 (10.3%) 0.715
	10 min		2/67 (3.0%)	5/184 (2.7%) 0.909 <sup>b</sup>
umbilical pH at birth, mean $\pm$ SD	219	7.28 $\pm$ 0.08	7.26 $\pm$ 0.08	0.089
Deaths, n/N (%)	pH < 7.15, n/N (%)	219	5/60 (8.3%)	19/159 (11.9%) 0.445
	Total	251	6/67 (9.0%)	11/184 (6.0%) 0.406
	Before 28 days	251	5/67 (7.5%)	8/184 (4.3%) 0.341 <sup>b</sup>
	After 28 days	251	1/67 (1.6%)	3/184 (1.7%) 0.938 <sup>b</sup>
Neonatal care				
	Neonatal Intensive care unit (NICU) hospitalization, n/N (%)	251	48/67 (71.6%)	118/184 (64.1%) 0.266
	length of stay in NICU, days, median (min - max)	149 <sup>c</sup>	6 (1 – 63)	6 (1 – 77) 0.120 <sup>a</sup>
	Length of hospital stay, days, median (min - max)	234 <sup>d</sup>	15 (3 – 113)	16 (3 – 130) 0.153 <sup>a</sup>
Neonatal complications				
	Respiratory distress, n/N (%)	249	37/67 (55.2%)	106/182 (58.2%) 0.669
	Hyaline membrane diseases, n/N (%)	251	17/67 (25.4%)	51/184 (27.7%) 0.712
	Bronchopulmonary dysplasia, n/N (%)	251	3/67 (4.5%)	26/184 (14.1%) 0.034 <sup>*</sup>
	Duration of ventilatory support, days, median (min - max)	234 <sup>d</sup>	1 (0 – 86)	1 (0 – 121) 0.119 <sup>a</sup>
	Brain abnormalities on MRI, n/N (%)	251	6/67 (9.0%)	18/184 (9.8%) 0.844
	Ventricular dilation, n/N (%)	251	0/67 (0.0%)	3/184 (1.6%) 0.293
	Intraventricular hemorrhage, n/N (%)	251	4/67 (6.0%)	4/184 (2.2%) 0.130
	Periventricular leukomalacia, n/N (%)	251	1/67 (1.5%)	3/184 (1.6%) 0.938
	Subependymal hemorrhage, n/N (%)	251	1/67 (1.5%)	7/184 (3.8%) 0.356
	Other, n/N (%)	251	0/67 (0.0%)	1/184 (0.5%) 0.545
	Ulcerative enterocolitis, n/N (%)	251	9/67 (13.4%)	20/184 (10.9%) 0.574
	Sepsis, n/N (%)	250	11/67 (16.4%)	40/183 (21.9%) 0.344
Composite morbidity endpoint <sup>e</sup> , n/N (%)	251	14/67 (20.9%)	46/184 (25.0%)	0.500

sIUGR: Selective IntraUterine Growth Retardation.

IUGR: IntraUterine Growth Retardation.

\*  $p$ -value < 0.05.

<sup>a</sup> Mann-Whitney U test (non-parametric variables).

<sup>b</sup> Fisher's exact test (insufficient numbers to perform Pearson's Chi2 test).

<sup>c</sup> Length of stay in the ICU, excluding ICU deaths and newborns who were not admitted to the ICU.

<sup>d</sup> Length of hospital stay and duration of ventilatory support excluding deaths.

<sup>e</sup> Composite criterion including the occurrence of one or more of the following: (i) neonatal death, (ii) stage III or IV intraventricular hemorrhage, (iii) periventricular white matter cyst, (iv) bronchopulmonary dysplasia, (v) stage II or III ulcerative enterocolitis.

**Table 4**

Comparison of neonatal outcomes between the 'selective intrauterine growth restriction' and 'intrauterine growth restriction' groups.

	sIUGR (N = 65) (Ref)	IUGR (N = 184)	Univariate analysis			Multivariate analysis <sup>a</sup>		
			OR	95% CI	P-value	Adjusted OR	95% CI	P-value
Apgar < 7, n/N (%)								
1 min	16/67 (23.9%)	59/184 (32.1%)	1.505	0.792 – 2.857	0.212	1.548	0.741 – 3.235	0.245
5 min	8/67 (11.9%)	19/184 (10.3%)	0.849	0.353 – 2.043	0.715	0.788	0.291 – 2.134	0.639
10 min	2/67 (3.0%)	5/184 (2.7%)	0.908	0.172 – 4.795	0.909	1.055	0.164 – 6.778	0.955
pH < 7.15, n/N (%)	5/60 (8.3%)	19/159 (11.9%)	1.493	0.531 – 4.196	0.447	1.514	0.491 – 4.671	0.471
NICU Hospitalizations, n/N (%)	48/67 (71.6%)	118/184 (64.1%)	0.708	0.384 – 1.303	0.267	0.582	0.233 – 1.454	0.247
Respiratory distress, n/N (%)	37/67 (55.2%)	106/182 (58.2%)	1.131	0.643 – 1.989	0.669	1.489	0.660 – 3.359	0.337
Brain abnormality on MRI, n/N (%)	6/67 (9.0%)	18/184 (9.8%)	1.102	0.418 – 2.906	0.844	0.930	0.297 – 2.909	0.901
Ulcerative enterocolitis, n/N (%)	9/67 (13.4%)	20/184 (10.9%)	0.786	0.339 – 1.824	0.575	0.647	0.227 – 1.846	0.415
Sepsis, n/N (%)	11/67 (16.4%)	40/183 (21.9%)	1.424	0.683 – 2.971	0.346	1.241	0.473 – 3.256	0.661
Neonatal death, n/N (%)	6/67 (9.0%)	11/184 (6.0%)	0.646	0.229 – 1.823	0.409	0.210	0.043 – 1.040	0.056
Composite endpoint, n/N (%)	14/67 (20.9%)	46/184 (25.0%)	1.262	0.641 – 2.483	0.501	0.946	0.317 – 2.827	0.921

sIUGR: Selective IntraUterine Growth Retardation.

IUGR: IntraUterine Growth Retardation.

<sup>a</sup> Adjusted multivariate analysis on criteria for which a difference was expected: gestational age at birth, birth weight, fetal sex, indication for birth (divided into 5 categories: spontaneous, fetal heart rhythm abnormalities, fetal Doppler abnormalities, fetal growth arrest, and other causes), and severity of Doppler abnormalities before birth (intermittent, permanent, or positive null diastole). The reference category is sIUGR.

composite endpoint of morbidity and mortality chosen as the primary endpoint was found to be almost identical between the two groups after statistical adjustment.

The body of data concerning the prognosis of fetuses with sIUGR in MCDA pregnancies was the subject of a systematic review of the literature with meta-analysis in 2017 [21]. Thirteen studies were included by the authors for a total of 610 patients. Nine of these studies reported fewer than 50 patients. This meta-analysis essentially reports on the differences in prognosis, especially in terms of in utero mortality according to the umbilical arterial diastole of the smaller twin at the time of diagnosis of sIUGR according to the Gratacós stages [19]. The heterogeneity of the data, the non-differentiation of the two twins in the analysis, and the very small number of studies actually reporting neonatal data do not allow a precise idea of the fate of newborns with sIUGR. To our knowledge, the 2017 study by Rustico et al. is the only study with a larger number of subjects than our study that reported neonatal morbidity data [17]. This study, whose objective was to describe the evolution of Doppler flows after diagnosis, included 140 patients, among whom 97 gave birth to two live twins. Seventeen newborns with sIUGR died during the neonatal period, and seven presented criteria of severe neonatal morbidity without specification of nature. The neurodevelopmental course of the surviving children was also precisely described in this study. In comparison, our study is more specifically focused on the neonatal morbidity and mortality of twins with sIUGR and thus allows us to provide more precise data on this period. Moreover, by comparing it with IUGR, which is better studied and whose neonatal implications are better known, our study provides a reasonable justification for the assimilation that is naturally made between these two pathologies in terms of neonatal morbidity and the mortality of the smaller twin. This extrapolation can be useful information for parents in the absence of more tangible scientific data.

The limitations of our study are related to its retrospective nature, the small size of the sIUGR group, and the absence of medium- and long-term data on the outcomes of the children's cases. There is also a potential selection bias related to the nature of our prenatal diagnosis unit, which specializes in the management of complications of twin pregnancies. Twin pregnancies complicated by sIUGR are thus referred to our center regardless of their severity, whereas only the most severe IUGR (of singletons) are referred to us. The heterogeneity of the data, particularly with regard to the term of diagnosis and birth, is also an obvious limitation for the interpretation of the results. The choice not to define a cut-off term for inclusion is justified by the need to obtain sufficient statistical power to allow a reliable

comparison of the two groups. The multivariate analysis, taking into account known factors influencing neonatal morbidity, adds to the reliability of this comparison. The exclusion of pregnancies for which IUGR occurred also introduces an obvious bias in the interpretation of the results since the most serious clinical situations are de facto not taken into account in the analysis. This methodological choice was made with the intention of focusing our study specifically on the neonatal morbidity and mortality of the smaller twin with sIUGR. Data regarding the antepartum period and the factors involved in the risk of in utero death is more numerous in the scientific literature [17,19,32–34].

Although our study focuses on the smallest twin of MCBA pregnancies with sIUGR, it is important to underline that this pathology leads to prematurity for both fetuses and therefore also involves the eutrophic twin. This information is of utmost importance and must be explained to the parents at the time of diagnosis.

Finally, the assimilation that our study suggests between sIUGR and IUGR is strictly limited to morbidity-mortality information in surviving newborns. In a recent study, the perinatal and two-year outcomes of twins born before 32 weeks were not significantly different between the monochorionic and bichorionic twin groups [35]. In other cohort studies, with inclusion to term, the number of sIUGRs was higher in monochorionic twins [36,37]. Furthermore, IUGR has been shown to be a risk factor for neonatal complications that is not independent of chorionicity [38] or birth term [39]. Some studies suggest that the combination of MCDA pregnancy and sIUGR is associated with negative neurological outcomes [40] and that morbidity is more related to the amount of growth retardation than to the growth gap between the two twins [41,42].

Fig. 1 XXXXXX.

Moreover, since our study is purely observational and retrospective, it does not allow us to determine to what extent the use of the same monitoring and extraction protocols for the two pathologies is justified during the antenatal period. Only interventional studies, whose implementation necessarily raises complex ethical questions, could provide answers on this subject.

In conclusion, the results of our study suggest that the neonatal prognosis of the smaller twin with sIUGR in the context of an MCDA pregnancy followed with an expectant attitude is not different from that of a neonate from a singleton pregnancy with IUGR. To better understand the prognosis of sIUGR, further larger studies should be conducted providing an additional comparison with dichorionic diamniotic pregnancies and a long-term neurological evaluation.

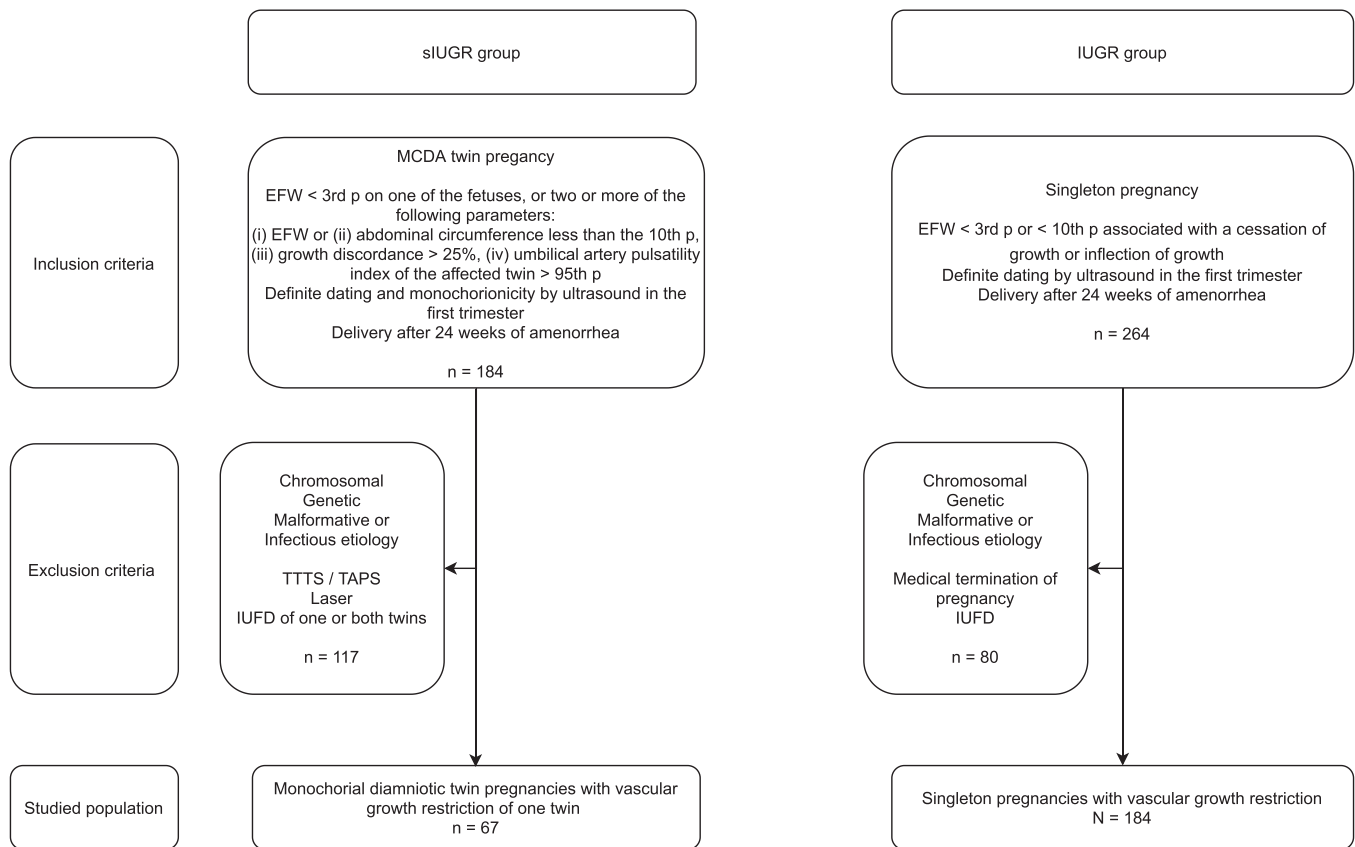


Fig. 1. Flow Chart.

## Funding statement

No funding was received for this work.

## Declaration of Competing Interest

The authors have no conflicts of interest to declare for this work.

## Acknowledgements

N/A

## References

- [1] Bennasar M, Eixarch E, Martinez JM, Gratacós E. Selective intrauterine growth restriction in monochorionic diamniotic twin pregnancies. *Semin Fetal Neonatal Med* 2017;22:376–82. doi: [10.1016/j.siny.2017.05.001](https://doi.org/10.1016/j.siny.2017.05.001).
- [2] Khalil A, Beune I, Hecher K, Wynia K, Ganzevoort W, Reed K, et al. Consensus definition and essential reporting parameters of selective fetal growth restriction in twin pregnancy: a Delphi procedure. *Ultrasound Obstet Gynecol* 2019;53:47–54. doi: [10.1002/uog.19013](https://doi.org/10.1002/uog.19013).
- [3] Gordijn SJ, Beune IM, Thilaganathan B, Papageorgiou A, Baschat AA, Baker PN, et al. Consensus definition of fetal growth restriction: a Delphi procedure. *Ultrasound Obstet Gynecol* 2016;48:333–9. doi: [10.1002/uog.15884](https://doi.org/10.1002/uog.15884).
- [4] Royal College of Obstetricians and Gynaecologists. Management of monochorionic twin pregnancy. *BJOG* 2017;124:e1–45. doi: [10.1111/1471-0528.14188](https://doi.org/10.1111/1471-0528.14188).
- [5] American college of obstetricians and gynecologists. ACOG practice bulletin No. 204: fetal growth restriction. *Obstetrics Gynecol* 2019;133:e97. doi: [10.1097/AOG.0000000000003070](https://doi.org/10.1097/AOG.0000000000003070).
- [6] Mari G, Hanif F. Intrauterine growth restriction: how to manage and when to deliver. *Clin Obstet Gynecol* 2007;50:497–509. doi: [10.1097/GRF.0b013e31804c96a9](https://doi.org/10.1097/GRF.0b013e31804c96a9).
- [7] Kovo M, Schreiber L, Ben-Haroush A, Wand S, Golan A, Bar J. Placental vascular lesion differences in pregnancy-induced hypertension and normotensive fetal growth restriction. *Am J Obstet Gynecol* 2010;202:561.e1–5. doi: [10.1016/j.ajog.2010.01.012](https://doi.org/10.1016/j.ajog.2010.01.012).
- [8] Chaddha V, Viero S, Huppertz B, Kingdom J. Developmental biology of the placenta and the origins of placental insufficiency. *Semin Fetal Neonatal Med* 2004;9:357–69. doi: [10.1016/j.siny.2004.03.006](https://doi.org/10.1016/j.siny.2004.03.006).
- [9] Levine RJ, Maynard SE, Qian C, Lim K-H, England LJ, Yu KF, et al. Circulating angiogenic factors and the risk of preeclampsia. *New England Journal of Medicine* 2004;350:672–83. doi: [10.1056/NEJMoa031884](https://doi.org/10.1056/NEJMoa031884).
- [10] Maynard SE, Venkatesha S, Thadhani R, Karumanchi SA. Soluble Fms-like tyrosine kinase 1 and endothelial dysfunction in the pathogenesis of preeclampsia. *Pediatr. Res.* 2005;57:1–7. doi: [10.1203/01.PDR.0000159567.85157.B7](https://doi.org/10.1203/01.PDR.0000159567.85157.B7).
- [11] Kinzler WL, Vintzileos AM. Fetal growth restriction: a modern approach. *Curr Opin Obstet Gynecol* 2008;20:125–31. doi: [10.1097/GCO.0b013e31804c96a9](https://doi.org/10.1097/GCO.0b013e31804c96a9).
- [12] Roberts JM, Hubel CA. The two stage model of preeclampsia: variations on the theme. *Placenta* 2009;30 Suppl A:S32–37. doi: [10.1016/j.placenta.2008.11.009](https://doi.org/10.1016/j.placenta.2008.11.009).
- [13] Denbow ML, Cox P, Taylor M, Hammal DM, Fisk NM. Placental angioarchitecture in monochorionic twin pregnancies: relationship to fetal growth, fetofetal transfusion syndrome, and pregnancy outcome. *Am J Obstet Gynecol* 2000;182:417–26. doi: [10.1016/s0002-9378\(00\)70233-x](https://doi.org/10.1016/s0002-9378(00)70233-x).
- [14] Fick AL, Feldstein VA, Norton ME, Wassel Fyr C, Caughey AB, Machin GA. Unequal placental sharing and birth weight discordance in monochorionic diamniotic twins. *Am J Obstet Gynecol* 2006;195:178–83. doi: [10.1016/j.ajog.2006.01.015](https://doi.org/10.1016/j.ajog.2006.01.015).
- [15] Lopriore E, Pasman SA, Klumper FJ, Middeldorp JM, Walther FJ, Oepkes D. Placental characteristics in growth-discordant monochorionic twins: a matched case-control study. *Placenta* 2012;33:171–4. doi: [10.1016/j.placenta.2011.12.004](https://doi.org/10.1016/j.placenta.2011.12.004).
- [16] Lewi L, Deprest J, Hecher K. The vascular anastomoses in monochorionic twin pregnancies and their clinical consequences. *Am J Obstet Gynecol* 2013;208:19–30. doi: [10.1016/j.ajog.2012.09.025](https://doi.org/10.1016/j.ajog.2012.09.025).
- [17] Rustico MA, Consonni D, Lanna M, Faiola S, Schena V, Scelsa B, et al. Selective intrauterine growth restriction in monochorionic twins: changing patterns in

- umbilical artery Doppler flow and outcomes. *Ultrasound Obstet Gynecol* 2017;49:387–93. doi: [10.1002/uog.15933](https://doi.org/10.1002/uog.15933).
- [18] Sacchi C, Marino C, Nosarti C, Vieno A, Visentin S, Simonelli A. Association of intrauterine growth restriction and small for gestational age status with childhood cognitive outcomes: a systematic review and meta-analysis. *JAMA Pediatr* 2020;174:772–81. doi: [10.1001/jamapediatrics.2020.1097](https://doi.org/10.1001/jamapediatrics.2020.1097).
- [19] Gratacós E, Levi L, Muñoz B, Acosta-Rojas R, Hernandez-Andrade E, Martinez JM, et al. A classification system for selective intrauterine growth restriction in monochorionic pregnancies according to umbilical artery Doppler flow in the smaller twin. *Ultrasound Obstet Gynecol* 2007;30:28–34. doi: [10.1002/uog.4046](https://doi.org/10.1002/uog.4046).
- [20] Townsend R, Khalil A. Twin pregnancy complicated by selective growth restriction. *Curr Opin Obstet Gynecol* 2016;28:485–91. doi: [10.1097/GCO.0000000000000326](https://doi.org/10.1097/GCO.0000000000000326).
- [21] Buca D, Pagani G, Rizzo G, Familiari A, Flacco ME, Manzoli L, et al. 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. *Ultrasound Obstet Gynecol* 2017;50:559–68. doi: [10.1002/uog.17362](https://doi.org/10.1002/uog.17362).
- [22] Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements—a prospective study. *Am J Obstet Gynecol* 1985;151:333–7. doi: [10.1016/0002-9378\(85\)90298-4](https://doi.org/10.1016/0002-9378(85)90298-4).
- [23] Khalil A, Beune I, Hecher K, Wynia K, Ganzevoort W, Reed K, et al. Consensus definition and essential reporting parameters of selective fetal growth restriction in twin pregnancy: a Delphi procedure. *Ultrasound Obstet Gynecol* 2019;53:47–54. doi: [10.1002/uog.19013](https://doi.org/10.1002/uog.19013).
- [24] Kontopoulos E, Chmait RH, Quintero RA. Twin-to-twin transfusion syndrome: definition, staging, and ultrasound assessment. *Twin Res Hum Genet* 2016;19:175–83. doi: [10.1017/thg.2016.34](https://doi.org/10.1017/thg.2016.34).
- [25] Gratacós E, Ortiz JU, Martinez JM. A systematic approach to the differential diagnosis and management of the complications of monochorionic twin pregnancies. *FDT* 2012;32:145–55. doi: [10.1159/000342751](https://doi.org/10.1159/000342751).
- [26] Mamelle N, Munoz F, Martin JL, Laumon B, Grandjean H. [Fetal growth from the AUDIPOG study. II. Application for the diagnosis of intrauterine growth retardation]. *J Gynecol Obstet Biol Reprod (Paris)* 1996;25:71–7.
- [27] Ego A. [Definitions: small for gestational age and intrauterine growth retardation]. *J Gynecol Obstet Biol Reprod (Paris)* 2013;42:872–94. doi: [10.1016/j.jgyn.2013.09.012](https://doi.org/10.1016/j.jgyn.2013.09.012).
- [28] French College of Gynecologists and Obstetricians. [Intra-uterine growth retardation: guidelines for clinical practice—Short text]. *J Gynecol Obstet Biol Reprod (Paris)* 2013;42:1018–25. doi: [10.1016/j.jgyn.2013.09.023](https://doi.org/10.1016/j.jgyn.2013.09.023).
- [29] Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr* 1978;92:529–34. doi: [10.1016/s0022-3476\(78\)80282-0](https://doi.org/10.1016/s0022-3476(78)80282-0).
- [30] Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Ann Surg* 1978;187:1–7. doi: [10.1097/0000658-197801000-00001](https://doi.org/10.1097/0000658-197801000-00001).
- [31] Jobe AH. The new bronchopulmonary dysplasia. *Curr Opin Pediatr* 2011;23:167–72. doi: [10.1097/MOP.0b013e3283423e6b](https://doi.org/10.1097/MOP.0b013e3283423e6b).
- [32] Ishii K, Murakoshi T, Takahashi Y, Shinno T, Matsushita M, Naruse H, et al. Perinatal outcome of monochorionic twins with selective intrauterine growth restriction and different types of umbilical artery Doppler under expectant management. *Fetal Diagn Ther* 2009;26:157–61. doi: [10.1159/000253880](https://doi.org/10.1159/000253880).
- [33] Ishii K, Murakoshi T, Hayashi S, Saito M, Sago H, Takahashi Y, et al. Ultrasound predictors of mortality in monochorionic twins with selective intrauterine growth restriction. *Ultrasound Obstet Gynecol* 2011;37:22–6. doi: [10.1002/uog.8846](https://doi.org/10.1002/uog.8846).
- [34] Khalil A, Beune I, Hecher K, Wynia K, Ganzevoort W, Reed K, et al. Consensus definition and essential reporting parameters of selective fetal growth restriction in twin pregnancy: a Delphi procedure. *Ultrasound Obstet Gynecol* 2019;53:47–54. doi: [10.1002/uog.19013](https://doi.org/10.1002/uog.19013).
- [35] Tosello B, Garbi A, Blanc J, Lorthe E, Foix-L'Hélias L, D'Ercole C, et al. The impact of chorionicity on pregnancy outcome and neurodevelopment at 2 years old among twins born preterm: the EPIPAGE-2 cohort study. *BJOG* 2021;128:281–91. doi: [10.1111/1471-0528.16170](https://doi.org/10.1111/1471-0528.16170).
- [36] Lewi L, Gucciardo L, Van Mieghem T, de Koninck P, Beck V, Medek H, et al. Monochorionic diamniotic twin pregnancies: natural history and risk stratification. *Fetal Diagn Ther* 2010;27:121–33. doi: [10.1159/000313300](https://doi.org/10.1159/000313300).
- [37] Fumagalli M, Schiavolin P, Bassi L, Groppo M, Uccella S, De Carli A, et al. The impact of twin birth on early neonatal outcomes. *Am J Perinatol* 2016;33:63–70. doi: [10.1055/s-0035-1556881](https://doi.org/10.1055/s-0035-1556881).
- [38] Hack KEA, Derks JB, Elias SG, Franx A, Roos EJ, Voerman SK, et al. Increased perinatal mortality and morbidity in monochorionic versus dichorionic twin pregnancies: clinical implications of a large Dutch cohort study. *BJOG* 2008;115:58–67. doi: [10.1111/j.1471-0528.2007.01556.x](https://doi.org/10.1111/j.1471-0528.2007.01556.x).
- [39] Coutinho Nunes F, Domingues AP, Vide Tavares M, Belo A, Ferreira C, Fonseca E, et al. Monochorionic versus dichorionic twins: are obstetric outcomes always different? *J Obstet Gynaecol* 2016;36:598–601. doi: [10.3109/01443615.2015.1116501](https://doi.org/10.3109/01443615.2015.1116501).
- [40] Smith NA, Wilkins-Haug L, Santolaya-Forgas J, Acker D, Economy KE, Benson CB, et al. Contemporary management of monochorionic diamniotic twins: outcomes and delivery recommendations revisited. *Am J Obstet Gynecol* 2010;203:133.e1–6. doi: [10.1016/j.ajog.2010.02.066](https://doi.org/10.1016/j.ajog.2010.02.066).
- [41] Garabedian C, Poulain C, Duhamel A, Subtil D, Houfflin-Debarge V, Deruelle P. Intrapartum management of twin pregnancies: are uncomplicated monochorionic pregnancies more at risk of complications than dichorionic pregnancies? *Acta Obstet Gynecol Scand* 2015;94:301–7. doi: [10.1111/aogs.12558](https://doi.org/10.1111/aogs.12558).
- [42] Papiernik E, Zeitlin J, Delmas D, Blondel B, Künzel W, Cattini M, et al. Differences in outcome between twins and singletons born very preterm: results from a population-based European cohort. *Hum Reprod* 2010;25:1035–43. doi: [10.1093/humrep/dep430](https://doi.org/10.1093/humrep/dep430).