

Influence of mode of delivery on perinatal outcome and neurodevelopment in monochorionic diamniotic twins: A single-center retrospective cohort study

Angel Chimenea¹, Lutgardo García-Díaz¹, and Guillermo Antiñolo Gil¹

¹Virgen del Rocio University Hospital

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Abstract

Objective: To study the influence of the mode of delivery in uncomplicated monochorionic diamniotic (MCDA) twins [?] 32 weeks of gestation. **Design:** Single-center retrospective cohort study. **Setting:** Department of Materno Fetal Medicine. Virgen del Rocio University Hospital. **Population or sample:** A total of 72 MCDA twins between 2012 and 2018. **Methods:** Outcomes were compared between women who underwent a trial of labor (TOL) (induced or spontaneous onset of labor) and those who underwent a planned cesarean section (PCS). **Main outcome measures:** (1) A composite of any of the following: neonatal death, 5-minute Apgar score <4, respiratory distress syndrome, bronchopulmonary dysplasia, sepsis, periventricular leukomalacia, intraventricular hemorrhage, and necrotizing enterocolitis. (2) Neurodevelopmental impairment (NDI) at 2 years of corrected age. **Results:** In this period, 42 women (58.3%) had a TOL and 30 women (41.7%) had a PCS. In the TOL group, 64.3% achieved vaginal delivery. The rate of successful vaginal delivery was similar regardless of whether the onset of labor was spontaneous or induced. Composite perinatal morbidity was higher in the PCS group (aOR 1.36, 95% CI 0.24-7.81) and, considering the onset of labor, it was more frequent in the spontaneous subgroup (8.3% vs. 0%). The rate of NDI was higher in the PCS group [10.2% vs. 4.9%, aOR 1.53 (95% CI 0.37-6.29)]. **Conclusions:** In uncomplicated MCDA twins at [?] 32 weeks of gestation, when the first twin is in vertex presentation, trial of labor is a safe approach with a successful outcome and high vaginal delivery rate.

1. Introduction

Compared to singleton pregnancies, twin pregnancies are at a higher risk for an adverse perinatal outcome^{[1]-[3]}. Hence, the optimal mode of delivery is a particularly contentious issue. A long-lasting debate keeps the controversy going; while some authors suggest that vaginal delivery is a safe option for uncomplicated twin pregnancies^{[4]-[6]}, other investigators recommend planned caesarean section (PCS) in order to avoid intrapartum complications, especially those derived from breech extraction^{[7]-[9]}.

Due to their idiosyncrasy, the dilemma in monochorionic diamniotic (MCDA) twins is even greater, as vascular anastomoses between fetal circulations can result in acute and dramatic hemodynamic intrapartum changes^{[10]-[12]}. But even in uneventful monochorionic pregnancies, likelihood of adverse perinatal outcomes is higher compared with singletons and dichorionic twin pregnancies^{[10],[13]-[14]}.

Although chorionicity has a significant influence on perinatal outcomes, most studies dealing with the mode of delivery in twins do not stratify this topic accordingly^{5,15}. Furthermore, published studies regarding the mode of delivery in MCDA pregnancies do not consider essential outcome issues as induction of labor when attempting vaginal delivery or neurodevelopment^{[16]-[23]}. Also, in most reports, the results are based on multicenter studies or national databases analysis, which makes them difficult to extrapolate, as there are no common and homogeneous obstetric policies. Neonatal criteria for defining morbidity are different, and in many cases do not cover all the main complications of MCDA pregnancies.

The purpose of this study was to investigate perinatal outcomes and 2-year-neurodevelopment for moderately to late preterm and early term MCDA twins with respect to the mode of birth, as well as to assess the safety of the induction of labor at a major tertiary center in Spain.

2. Material and Methods

Study design, setting and population

This is a retrospective cohort study conducted at Virgen del Rocío University Hospital of Seville (a tertiary referral center with about 6000 births per year), including all women with uncomplicated MCDA pregnancies who had a birth at 32.0 – 37.6 weeks of gestation from January 2012 to December 2018.

Chorionicity was determined by first-trimester ultrasonography and confirmed after birth by pathological examination. In all cases a detailed anomaly scan was performed at 18.0 – 21.6 weeks. Specific management protocols for MCDA twins were determined locally following national and international guidelines, as those established by the Royal College of Obstetricians and Gynaecologists (RCOG)^[24] or the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)^[25].

Cases were classified into trial of labor (TOL) or PCS groups depending on the intended method of delivery. A TOL was planned if twin A was in vertex presentation after 32 weeks of gestation, estimated fetal weight was at least 1500 g, and there was no contraindication for vaginal delivery (non-vertex first twin, at least two previous CS, weight discordance > 15% when first twin was smaller, vasa previa, and/or any other condition like active herpes genital infection). Deliveries were included as TOL when the onset of labor was spontaneous or induced, and in all cases both fetuses were monitored intrapartum by continuous cardiotocography. In cases of non-vertex presentation of the second twin, breech extraction was performed by a senior obstetrician. The maximum time to perform an emergent CS was 10 minutes after decision.

A PCS was in most cases established when the first twin was in a non-vertex presentation. In no cases, a PCS was performed because of maternal request. At least two obstetricians and neonatologists were always present in the delivery room (from the second stage of labor) as well as in the operating room.

Outcomes

The primary outcome was a composite of perinatal morbidity, with any of the following: neonatal death, 5-minute Apgar score of <4, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), sepsis, periventricular leukomalacia (PVL), intraventricular hemorrhage (IVH) and necrotizing enterocolitis (NE). 5-minute Apgar score of < 7 was registered as well.

Like other authors^[23], we did not use pH at birth as a primary outcome, as we found a significant interaction with 5-minute Apgar score of <4.

Secondary outcome included neurodevelopmental impairment (NDI) at 2 years of corrected age. Thus, we performed a standardized neurological examination on children at a corrected age of 2 years. For this purpose, we used the revised Brunet-Lézine scale to identify NDI. This scale includes four domains of psychomotor development: language, sociability, as well as gross and fine motor function. Infants were classified as having NDI if they had a global developmental quotient (DQ) on the revised Brunet-Lézine scale of < 85, or level 3 cerebral palsy (CP), and severe NDI was defined with a DQ of < 60.

Enrolment criteria

We successively enrolled all pregnant women with MCDA twins that met the criteria summarized in table 1. We only included MCDA twin pregnancies when both fetuses were alive after 32 weeks of gestation.

Exposures

The exposure was the planned mode of delivery in uncomplicated MCDA twins, which was established before the onset of labor. This was categorized as PCS or TOL, including spontaneous vaginal vertex deliveries, assisted vaginal birth (forceps, Thierry's spatula, and ventouse deliveries), breech extraction of the second

twin, and emergent cesarean section. Breech extraction was performed in MCDA twins when gestational age at delivery was 32 weeks or greater, in the absence of a previous CS, and intertwin weight discordance was less than 15%.

In case of induction of labor, PCS, or breech extraction, informed consent was provided and explained, detailing the risks and benefits of each technique.

Data source

Maternal demographic data, perinatal outcome, and neurodevelopment information were documented. Data were extracted from the electronic health record and ultrasound data from ViewPoint software. Later, anonymized data analysis was provided by a randomly generated study identifier.

Statistical analysis

Statistical analysis was performed using the SPSS 25.0 software package (SPSS Inc., Chicago, IL), and statistical significance was assumed at $p < 0.05$. All hypothesis tests were two-sided.

Values were expressed as mean $\pm$ standard deviation (SD) since data were normally distributed, and categorical variables were expressed as numbers and percentages. Univariable comparisons of categorical variables were performed using a chi-squared test or Fisher's exact test. Comparison of normally distributed continuous variables was performed using Student's T-test, and non-normally distributed variables with the Mann-Whitney U-test. Binary logistic regression models were used to calculate odds ratios (OR) and 95% confidence intervals (CI).

Ethical approval

Institutional Review Board approval of this retrospective study was obtained from the Andalusian Ethical Committee (Spain) on 11 October 2019 (1318-N-19). The requirement for informed consent was waived because the data were de-identified.

3. Results

Participants characteristics

There were 43,914 births between 2012 and 2018 at Virgen del Rocío University Hospital (Seville, Spain). Over these 6-year period, there were 84 MCDA twin births later than 30 weeks of gestation of pregnancies who were fully followed-up in our department, from the first-trimester ultrasound to delivery.

Of those, cases with twin-to-twin transfusion syndrome (TTTS) ($n = 5$), stillbirth ($n = 3$), severe preeclampsia ($n = 1$), severe intrauterine growth restriction (IUGR) ($n = 2$), and gestational age at birth < 32 weeks ($n=5$) were excluded from the study (some of the pregnancies shared more than one of the above criteria). In total, 12 pregnancies were excluded.

The final analysis included 72 uncomplicated MCDA twin pregnancies: 42 women (58.3%) in the TOL group and 30 women (41.7%) in the PCS group. The flow chart of participant enrolment is shown in Figure 1.

The demographic, clinical, and neonatal characteristics are described in table 2. No differences were found in most baseline characteristics, including maternal age, smoking habit, previous delivery, weight, use of artificial reproductive techniques (ART), gestational diabetes, or pre-gestational diabetes mellitus. No statistically significant differences were found regarding mean gestational age at birth (TOL: 36.2 weeks vs. PCS: 35.3 weeks, $p=0.15$). The mean weight at birth was lower in the PCS group, both for the first twin (2,228 g vs. 2,413 g, $p=0.07$) and the second one (2,134 g vs. 2,385 g, $p=0.02$). There were no maternal deaths or severe morbidity in this study.

Obstetric outcomes in TOL and PCS groups

In the TOL group, 64.3% of women achieved vaginal delivery. Combined delivery (vaginal delivery of the first twin and intrapartum CS of the second twin) was performed in only one woman (2.4%). Fourteen cases

(33.3%) from the TOL group were delivered via emergency CS because of non-reassuring fetal status ($n = 7$) or labor arrest ($n = 7$).

For pregnancies assigned to TOL group, 57.1% of pregnancies (24/42) had induction of labor, in most cases to avoid delivery above 37.6 weeks, and 42.9% (18/42) had a spontaneous onset of labor. The rate of successful vaginal delivery was higher in the spontaneous onset of labor subgroup (72.2% vs. 58.3%, $p=0.35$).

Perinatal outcomes in TOL and PCS groups

Table 3 lists the incidence of adverse perinatal outcomes as well as the association between perinatal factors for fetuses born in each group. The composite perinatal morbidity was observed in 3.6% of pregnancies (3/84) in at least one fetus in the TOL group, and in 8.3% of pregnancies (5/60) in the PCS group [aOR 1.36 (95% CI 0.24-7.81), $p=0.22$]. The rate of composite perinatal morbidity was higher in the PCS group for the second twin [5.0% vs. 2.4%, aOR 3.20 (95% CI 0.16-65.88)], yet these differences did not reach statistical significance ($p=0.16$). None of the eight cases in which breech extraction was performed had a perinatal complication.

Composite perinatal morbidity declined significantly after 32 weeks of gestation, remaining under 20% until 37 weeks (figure 2). Due to the low frequency of the different items included in terms of composite perinatal morbidity, we did not find significant differences between the two groups in any of them. No cases resulted in neonatal death in either group.

In the subgroup analysis, we compared the outcomes regarding the onset of labor when a vaginal delivery was attempted (table 4). The mean gestational age was significantly lower in the spontaneous delivery group, since no labor induction was performed by protocol below 35 weeks (35.4 vs. 36.6 weeks, $p=0.001$). Within the TOL group, the rate of composite perinatal morbidity was higher in the spontaneous trial of labor subgroup (8.3% vs. 0%, $p=0.08$), essentially related to an IVH event occurred in both twins born from the same delivery at 34.2 weeks.

Finally, we performed a comparison between the perinatal outcomes of induced onset of labor group vs. PCS group (table 5). We found a higher composite perinatal morbidity in the PCS group, although without significant differences (8.3% vs. 0%, $p=0.06$). These differences were maintained in the stratification by gestational age and order of birth.

2-year-neurodevelopment status

Finally, we studied the neurodevelopment of the children at 2-year-age. Data is available in tables 3 and 4. Neurodevelopment status data were available for 140 children of the initial cohort: 81 from the TOL group and 59 from the PCS group. Among these infants, the rate of NDI was slightly higher in the PCS group, without reaching statistical significance [10.2% vs. 4.9%, aOR 1.53 (95% CI 0.37-6.29), $p=0.26$]. We also found a higher rate of severe NDI in the PCS group (3.4% vs. 0%, $p=0.18$).

Regarding the mode of onset of labor, we found a lower NDI rate in the induced onset group compared to spontaneous onset of labor group (0% vs. 11.8%, $p=0.03$), with no events of severe NDI. The rate of NDI was also lower in the induced onset of labor group compared to the PCS group (10.2% vs. 0%, $p=0.03$), without reaching significant differences in the appearance of severe NDI events (3.4% vs. 0%, $p=0.50$).

4. Discussion

Main findings

In this study, the results indicated that TOL is not associated with a higher risk of adverse perinatal outcomes or NDI at 2 years in uncomplicated MCDA twins when compared to a PCS. In the PCS group, the composite perinatal morbidity was higher (aOR 1.36, 95% CI 0.24-7.81), also finding a slightly higher rate of NDI at 2 years (10.2% vs. 4.9%) and severe NDI (3.4% vs. 0%). Attempted vaginal delivery is therefore shown to be a safe strategy with a high vaginal delivery rate.

Additionally, regarding the onset of labor in TOL group, induction of labor has been shown to be a safe strategy when performed above 35. In our study, we found a higher perinatal morbidity in the spontaneous trial of labor subgroup, with a higher rate of 2-year-NDI. Nevertheless, the composite perinatal morbidity in both subgroups was lower than that found after PCS. The vaginal delivery rate in the TOL group was higher in the spontaneous onset of labor subgroup.

The main clinical implication of this study is to provide evidence and support to parents and practitioners when deciding the mode of delivery and onset of labor in uncomplicated MCDA twins after 32 weeks of gestation.

Interpretation and comparison to current literature

MCDA twins are considered to be at highest risk of perinatal morbidity and mortality because of acute hemodynamic intrapartum changes mediated by placental vascular anastomoses^{[10]-[11]}. However, due to a lack of evidence, there is no clear consensus regarding the optimal mode of delivery in uncomplicated twins. Despite the relevance of chorionicity, most studies addressing the contribution of the mode of delivery in perinatal morbidity have not been stratified accordingly. Furthermore, relevant aspects such as the mode of onset of labor or long-term neurodevelopment have not been taken into consideration.

To date, only eight studies have taken chorionicity into account when analyzing the optimal mode of delivery in uncomplicated twins, with disparate designs and neonatal morbidity criteria^{[16]-[23]}. Of the eight studies, four were secondary analysis of previous studies. None of them considered the mode of onset of labor in the TOL group or long-term NDI. The most relevant data of each study are summarized in table 6. Our findings are consistent with those reported in the above-mentioned studies, demonstrating that attempted vaginal delivery for uncomplicated MCDA twins is a safe management option, when performed by a trained obstetric team, and has a low perinatal morbidity rate. Therefore, when first twin is in vertex presentation, PCS does not seem to be the strategy to avoid perinatal adverse events in uncomplicated MCDA pregnancies after 32.0 weeks, but rather shows a slight increase in them (aOR 1.36, 95% CI 0.24-7.81).

The gestational age at delivery in the pregnancies included in the different studies is highly variable, ranging from 24.0 to 38.6 weeks. In our study, we decided to include moderate to late preterm births (32.0 – 36.6 weeks) to avoid masking a protective effect of cesarean section in that range of gestational age.

The impact of the mode of delivery in twins on 2-year-neurodevelopment was studied by Asztalos et al. in 2016^[26]. The authors performed a secondary analysis of the *Twin Birth Study*, a large randomized controlled trial designed to compare planned vaginal delivery and PCS^[5]. This study finally included 2,323 pregnancies, of which 555 were MCDA. Although they do not stratify the data in relation to chorionicity, the authors conclude that a policy based in PCS provides no benefit to children at 2 years of age [5.99% vs. 5.83%, OR 1.04 (95% CI 0.77-1.41), p=0.79]. Our study yields similar results, although the NDI rate is slightly higher in PCS group compared to TOL and their different onset modalities (spontaneous or induced). However, the rate of 2-year-NDI is similar to that reported by other authors when a selective analysis of MCDA pregnancies is performed^[27].

Strengths and limitations

The main strength of this study is that all pregnancies included were fully evaluated and delivered in a single tertiary center, with a long tradition of vaginal delivery and breech extraction of the second twin.

To our knowledge, this is the first study considering the mode of onset of labor as well as 2-years-neurodevelopment. Although the study population is not large, we were able to define more detailed and accurate perinatal outcome measures than it is possible to do with registry-based data. Furthermore, this is a primary analysis, and not a subgroup analysis of a previous larger study.

Though retrospective studies are limited by confounders, it is not possible to develop this study as a randomized controlled trial for ethical reasons. In our center, at least two obstetricians and two neonatologists

were always present at birth, and an operating room was available for emergency CS if required; therefore, the results can be extrapolated to centers that meet the same conditions.

5. Conclusion

In uncomplicated monochorionic diamniotic twins at [?] 32 weeks of gestation, when first twin is in vertex presentation, trial of labor is a safe management option in terms of perinatal morbidity as well as long-term neurodevelopment, with a high vaginal delivery rate.

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Figures

Figure 1. Flow chart of participant enrolment

Figure 2. Composite perinatal morbidity regarding to gestational age and planned mode of delivery

Disclosure of interest

Authors have no conflict of relevant financial, personal, political, intellectual or religious interests to declare.

Contribution to authorship

A.C., L.G., and G.A. contribute to conception and design. A.C. was responsible to acquisition of data. A.C., L.G., and G.A. contribute to analysis and interpretation of data. All authors contribute to drafting the article or revising it critically for important intellectual content. All authors contributed to the write up of the manuscript and approved the final version for submission.

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Details of ethics approval

Institutional Review Board approval of this retrospective study was obtained from the Andalusian Ethical Committee (Spain) on 11 October 2019. The requirement for informed consent was waived because the data were de-identified.

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Table 1. Enrolment criteria

Inclusion criteria	Exclusion criteria
TOL between 32.0 and 37.6 weeks	Stillbirth Congenital anomaly Severe preeclampsia Antepartum cardiotocography pathology Severe intrauterine growth restriction (IUGR) Selective IUGR Twin-to-twin transfusion syndrome Twin anemia-polycythemia sequence Gestational age less than 32 weeks or greater than 38 at the time of delivery Uncertainty about the gestational age at birth
Spontaneous onset of labor (between 32.0-37.6 weeks) or induced onset of labor (between 35.0-37.6 weeks) in uncomplicated MCDA twin pregnancy with no contraindication for vaginal delivery.	
PCS between 32.0 and 37.6 weeks	
Spontaneous onset of labor in uncomplicated MCDA twin pregnancy with contraindication for vaginal delivery.	
PCS regarding to: Previous CS Positional placental anomaly First twin in non-vertex presentation Another obstetric non-urgent indication for PCS	

Table 2. Maternal baseline characteristics and delivery data in TOL and PCS groups

Variable	TOL group n=42 (58.3%)	PCS group n=30 (41.7%)	P value
Maternal age, years	40 ± 4.96	40 ± 6.23	0.83

Maternal weight, kilograms	65.9 ± 16.77	63.4 ± 12.84	0.78
Previous CS, n(%)	1 (2.4%)	10 (33.3%)	<0.001
Previous vaginal birth, n(%)	18 (42.9%)	8 (26.7%)	0.16
IVF pregnancy, n(%)	8 (19.0%)	6 (20.0%)	0.92
Pregestational diabetes, n(%)	0 (0%)	1 (3.3%)	0.42
Gestational diabetes, n(%)	3 (7.1%)	1 (3.3%)	0.49
Smoking habit, n(%)	11 (26.2%)	8 (26.7%)	0.96
Gestational age at delivery, weeks	36.2 ± 1.28	35.3 ± 2.05	0.15
Intertwin birth interval, min	5.0 ± 6.10	2.0 ± 2.41	<0.001
First twin birthweight, grams	2,413 ± 384.10	2,228 ± 456.68	0.07
Second twin birthweight, grams	2,385 ± 437.22	2,134 ± 447.62	0.02

Table 3. Perinatal outcomes and NDI according to the planned mode of delivery

	Overall n=144	TOL group n=84	PCS group n=60	p value	OR (95% CI)	aOR (95% CI)**
Composite perinatal morbidity, n(%)	8 (5.6)	3 (3.6)	5 (8.3)	0.22	2.46 (0.56-10.69)	1.36 (0.24-7.81)
First twin	4 (5.6)	2 (4.8)	2 (3.3)	0.73	1.43 (0.19-10.75)	0.77 (0.074-8.04)
Second twin	4 (5.6)	1 (2.4)	3 (5)	0.16	4.56 (0.45-46.11)	3.20 (0.16-65.88)
> 34 week's	4/124 (3.2)	2/80 (2.5)	2/44 (4.5)	0.54	1.86 (0.25-13.66)	4.69 (0.85-25.81)
> 36 week's	3/86 (3.5)	1/56 (1.8)	2/30 (6.7)	0.24	3.93 (0.34-45.22)	5.21 (0.49-55.63)
5-minute Apgar score <4	0	0	0	-	*	*
5-minute Apgar score <7	1 (0.7)	1 (1.2)	0	>0.99	*	*
Neonatal death	0	0	0	-	*	*

Respiratory morbidity (respiratory distress syndrome and/or broncho-pulmonary dysplasia)	0	0	0	-	*	*
Intraventricular hemorrhage	5 (3.5)	2 (2.4)	3 (5.0)	0.40	2.16 (0.35-13.33)	1.64 (0.19-14.57)
Periventricular leukomalacia	1 (0.7)	0	1 (1.7)	0.42	*	*
Necrotizing enterocolitis	1 (0.7)	0	1 (1.7)	0.42	*	*
Sepsis	0	0	0	-	*	*
2-year-Neurodevelopmental impairment, n(%)	10/140 (7.1)	4/81 (4.9)	6 / 59 (10.2)	0.26	2.11 (0.57-7.84)	1.53 (0.37-6.29)
Severe neurodevelopmental impairment	2/140 (1.4)	0	2 / 59 (3.4)	0.18	*	*

* OR cannot be calculated reliably due to zero events in at least one group.

**Adjusted for birth weight (per gram) and gestational age (per day).

Table 4. Perinatal outcomes and NDI according to the onset of labor in TOL group

	Overall n=84	Induced onset of labor n=48	Spontaneous onset of labor n=36	p value
Gestational age at delivery, weeks ($\pm$ SD)	36.2 $\pm$ 1.28	36.6 $\pm$ 0.70	35.4 $\pm$ 1.39	0.001
Composite perinatal morbidity, n(%)	3 (3.6)	0	3 (8.3)	0.08
First twin	2 (4.8)	0	2 (11.1)	0.18
Second twin	1 (2.4)	0	1 (5.6)	0.43
> 34 week's	2/80 (2.5)	0/48	2/32 (6.3)	0.16
> 36 week's	1/56 (1.8)	0/42	1/14 (7.1)	0.25
5-minute Apgar score <4	0	0	0	-

5-minute Apgar score <7	1 (1.2)	0	1 (2.9)	0.43
Neonatal death	0	0	0	-
Respiratory morbidity (respiratory distress syndrome and/or bronchopulmonary dysplasia)	0	0	0	-
Intraventricular hemorrhage	2 (2.4)	0	2 (5.6)*	0.18
Periventricular leukomalacia	0	0	0	-
Necrotizing enterocolitis	0	0	0	-
Sepsis	0	0	0	-
2-year-Neurodevelopmental impairment, n(%)	4/81 (4.9)	0/47	4/34 (11.8)	0.03
Severe neurodevelopmental impairment	0/81	0/47	0/34	-

Table 5. Perinatal outcomes and NDI in PCS group compared to induced onset of labor subgroup

	Overall n=108	Induced onset of labor n=48	PCS n=60	p value
Composite perinatal morbidity, n(%)	5	0	5 (8.3)	0.06
First twin	2	0	2 (3.3)	0.50
Second twin	3	0	3 (5)	0.25
> 34 week's	2	0/48	2/44 (4.5)	0.23
> 36 week's	2	0/42	2/30 (6.7)	0.17
5-minute Apgar score <4	0	0	0	-
5-minute Apgar score <7	0	0	0	-
Neonatal death	0	0	0	-
Respiratory morbidity (respiratory distress syndrome and/or bronchopulmonary dysplasia)	0	0	0	-

Intraventricular hemorrhage	3	0	3 (5.0)	0.25
Periventricular leukomalacia	1	0	1 (1.7)	>0.99
Necrotizing enterocolitis	1	0	1 (1.7)	>0.99
Sepsis	0	0	0	-
2-year-Neurodevelopmental impairment, n(%)	6/106 (5.7)	0 / 47	6/59 (10.2)	0.03
Severe neurodevelopmental impairment	2/106 (1.9)	0 / 47	2/59 (3.4)	0.50

Table 6. Selective analysis of uncomplicated MCDA twins delivery in terms of composite perinatal morbidity

		Design of study	Centers involved	GA	n	TOL	Planned CS	Difference induced labor from spontaneous onset	Items included	OR (CI 95%)	p	
<i>Sau et al. 2006</i>	Retrospective cohort study	Retrospective cohort study	Single-center	[?] 24 weeks	60	Not defined	Not defined	No	5-min Apgar score, umbilical pH, RDS, mortality, ventilation	- (-)	(-)	
<i>Hack et al. 2011</i>	Secondary analysis of a retrospective cohort study	Secondary analysis of a retrospective cohort study	Multicenter	[?] 32 weeks	902	752	150	No	5-min Apgar score, pH, RDS, IUFD, mortality	2.0 (1.0-4.2)	(-)	

		Design of study	Centers involved	GA	n	TOL	Planned CS	Difference in- duced labor from spon- ta- neous onset	Items included	OR (CI 95%)	p	
<i>Hoffmann et al. 2012</i>	Retrospective cohort study	Retrospective cohort study	Multicenter	36 weeks	115	63	52	No	5-min Apgar score, pH, mortality	0.9 (0.3- 3.0)	0.83	
<i>Weisz et al. 2012</i>	Retrospective cohort study	Retrospective cohort study	Single- center	35+0- 37+6 weeks	89	38	511	No (only in average of vaginal deliv- ery, not morbidity)	5-min Apgar score, pH, RDS, sepsis, CNS, mortality	- (-)	0.24	

		Design of study	Centers involved	GA	n	TOL	Planned CS	Difference in- duced labor from spon- ta- neous onset	Items included	OR (CI 95%)	p	
<i>Yamashita et al. 2014</i>	Retrospective co- hort study	Retrospective co- hort study	Single- center	[?] 36 weeks	295	187	108	No	5- min Ap- gar scores < 7, IUFD after 36 weeks' ges- ta- tion, neona- tal death, um- bili- cal artery pH < 7.1, hy- poxic is- chemic en- cephalopa- thy, meco- nium aspi- ra- tion syn- drome, res- pira- tory dis- tress syn- drome, or acute feto- fetal hemorrhage	0.4 (0.1- 2.0)	0.29	

		Design of study	Centers involved	GA	n	TOL	Planned CS	Difference in- duced labor from spon- ta- neous onset	Items included	OR (CI 95%)	p	
<i>Ylilehto et al. 2017</i>	Secondary analy- sis of a retro- spec- tive cohort study	Secondary analy- sis of a retro- spec- tive cohort study	Single- center	[?] 37 weeks	73	59	14	No	5-min Apgar < 4, 5-min Apgar < 7, umbili- cal artery pH < 7.05 Y < 7.00, NICU admission	- (-)	>0.99	

		Design of study	Centers involved	GA	n	TOL	Planned CS	Difference in- duced labor from spon- ta- neous onset	Items included	OR (CI 95%)	p	
<i>Ylilehto et al. 2020</i>	Secondary analy- sis of a retro- spec- tive cohort study	Secondary analy- sis of a retro- spec- tive cohort study	Single- center	Not speci- fied to this cohort (pri- mary cohort – mono and di- chori- onic: 32+0– 36+6 weeks of gestation)	55	40	15	No	5-min Apgar < 4, 5-min Apgar < 7, umbili- cal artery pH < 7.05, NICU admis- sion, intrac- erebral hemor- rhage gr. III-IV, respi- ratory mor- bidity, com- posite neona- tal morbidity,	- (-)	0.18	

		Design of study	Centers involved	GA	n	TOL	Planned CS	Difference in- duced labor from spon- ta- neous onset	Items included	OR (CI 95%)	p	
<i>Aviram et al. 2020</i>	Secondary analy- sis of a ran- dom- ized, con- trolled trial (Twin Birth Study, Barret et al. 2013)	Secondary analy- sis of a ran- dom- ized, con- trolled trial (Twin Birth Study, Barret et al. 2013)	Multicenter	32+0- 37+6 weeks	670	324	346	No	5-min Apgar < 4, Still- born, neona- tal death, pri- mary, , umbili- cal artery pH < 7.0, NICU admis- sion > 48h, as- sisted ventila- tion, NEC, PVL, com- posite outcome	- (-)	0.25	

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