Original Research

Survival Without Severe Neonatal Morbidity in Very Preterm Twins According to Planned Mode of Delivery

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OBJECTIVE: To assess survival to discharge without severe neonatal morbidity by planned mode of delivery for twins born before 32 weeks of gestation.

METHODS: The JUMODA (JUmeaux MODe d'Accouchement) study was a French national prospective, population-based, cohort study of twin deliveries conducted from February 2014 to March 2015. This planned secondary analysis included diamniotic twin pregnancies from 26 0/7 through 31 6/7 weeks of gestation. Exclusion criteria included contraindications to vaginal delivery and situations for which planned cesarean delivery is favored, and neonatal prognosis depends largely on the underlying pathology rather than the planned mode of delivery. The primary outcome was survival to discharge without severe neonatal morbidity (bronchopulmonary dysplasia, grade 3 or grade 4 intraventricular hemorrhage, periventricular leukomalacia, stage 2 or stage 3 necrotizing enterocolitis). The association between planned mode of delivery and primary outcome was assessed by multivariate Poisson regression model. A propensity-score approach with inverse probability of treatment weighting also was performed to control for indication bias. Subgroup analyses according to birth order and sensitivity analyses limited to spontaneous preterm births only were performed.

RESULTS: Among 424 very preterm twin pregnancies, 192 (45.3%) had a planned cesarean delivery and 232 (54.7%) had a planned vaginal delivery. Survival to discharge without severe morbidity did not differ in the two groups: 308 of 384 (80.2%) after planned cesarean and 375 of 464 (80.8%) after planned vaginal delivery (crude relative risk 0.99; 95% CI 0.91–1.15; adjusted relative risk 1.02; 95% CI 0.93–1.11). After applying inverse probability of treatment weighting, planned cesarean delivery still was not associated with higher survival to discharge without severe neonatal morbidity than planned vaginal birth (relative risk 1.11; 95% CI 0.84–1.46). Subgroup and sensitivity analyses showed similar results.

CONCLUSION: Planned cesarean delivery for very preterm twins is not associated with higher survival to discharge without severe neonatal morbidity than planned vaginal delivery. These results suggest that very preterm delivery should not be considered a per se indication for planned cesarean in twin pregnancies.

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Although twin pregnancies account for only 3% of all births in both the United States[1] and France,[1,2] they have complications more often than singleton pregnancies do and account for about one third of the very preterm deliveries in high-resource countries.

The most recent and contributive neonatal data about twin pregnancies–from the Twin Birth Study[3] and the JUMODA (JUmeaux MODe d'Accouchement) study[4]–did not show that neonatal mortality and morbidity rates differed according to the planned mode of delivery for twins born between 32 and 39 weeks of gestation. Controversy, nonetheless, persists about the planned mode of delivery for twins born before 32 weeks of gestation. No randomized controlled trials have compared planned vaginal and cesarean deliveries in this population. The results of some large retrospective population-based studies have shown an increased risk of neonatal morbidity, mainly for the second twin, after vaginal deliveries compared with cesarean deliveries.[3–6] But these studies were limited by selection bias[3–5] and by their comparison by the actual mode of delivery rather than the planned mode of delivery.[3,4,6] The few retrospective studies that assessed the planned mode of delivery have reported contradictory results for neonatal morbidity between groups.[7,8]

Consequently, the conclusions of the American[9] and French[10] guidelines that rely on these low levels of evidence both consider the data insufficient to recommend one planned mode of delivery rather than the other for very preterm twins.

The French nationwide prospective population-based cohort study of twin pregnancies, JUMODA, was specifically designed to assess perinatal morbidity and mortality in twins according to the planned mode of delivery and offered the opportunity to conduct analyses for very preterm twin pregnancies with high-quality data. The aim of this planned secondary analysis of the JUMODA cohort was to assess survival to discharge without severe neonatal morbidity according to the planned mode of delivery for twins born before 32 weeks of gestation.

METHODS

All study participants were part of JUMODA, a nationwide, observational, prospective, population-based study conducted from February 10, 2014, through March 1, 2015, in 176 French maternity units that each performed more than 1,500 annual deliveries. Detailed information regarding the participating women and maternity units has previously been reported.[11] This cohort, specially designed to assess the effect of the planned mode of delivery and of delivery management on perinatal outcomes in twin pregnancies, prospectively enrolled 8,823 women at or after 22 weeks of gestation immediately after delivery. Given the absence of solid evidence supporting one management policy over the other, French guidelines allow both planned cesarean delivery and planned vaginal delivery for very preterm twin pregnancies, depending on the situation and the obstetric team's preference.[10]

For this planned secondary analysis of the JUMODA cohort, we included twin pregnancies from 26 0/7 weeks of gestation because, during the study period, active antenatal care, including the willingness to perform a cesarean delivery for fetal indication between 24 and 26 weeks of gestation, was not general practice in France. It differed quite substantially from one maternity ward to another. Situations with contraindications to vaginal delivery were excluded (first twin in transverse presentation, repeated previous cesarean deliveries, or maternal contraindications). Other exclusion criteria were an underlying pathology for which a planned cesarean delivery is indicated and associated with neonatal prognosis, such as suspected fetal growth restriction for either twin, twin–twin transfusion syndrome, or abnormal fetal heart rate, and in utero fetal death for either twin (Fig. 1).

The exposure of interest was the planned mode of delivery, with planned vaginal delivery as the reference group. The planned mode of delivery was defined prospectively by the obstetrician who performed the delivery. Immediately after delivery, obstetricians completed a detailed web-based questionnaire about the planned mode of delivery, indications for planned cesarean delivery or induction of labor, and details about the delivery management, and classified it as a planned cesarean delivery or planned vaginal delivery.

Research nurses collected data about maternal characteristics, medical history, pregnancy complications, and neonatal health.

The primary outcome was survival to discharge without severe neonatal morbidity. This outcome was defined as the number of children discharged alive from the hospital (relative to the number of fetuses alive at the beginning of labor) without severe neonatal morbidity, which was defined as any of the following: grade 3 or grade 4 intraventricular hemorrhage confirmed by ultrasonography; periventricular leukomalacia; stage 2 or stage 3 necrotizing enterocolitis according to Bell's staging[12]; and bronchopulmonary dysplasia, defined as the need for

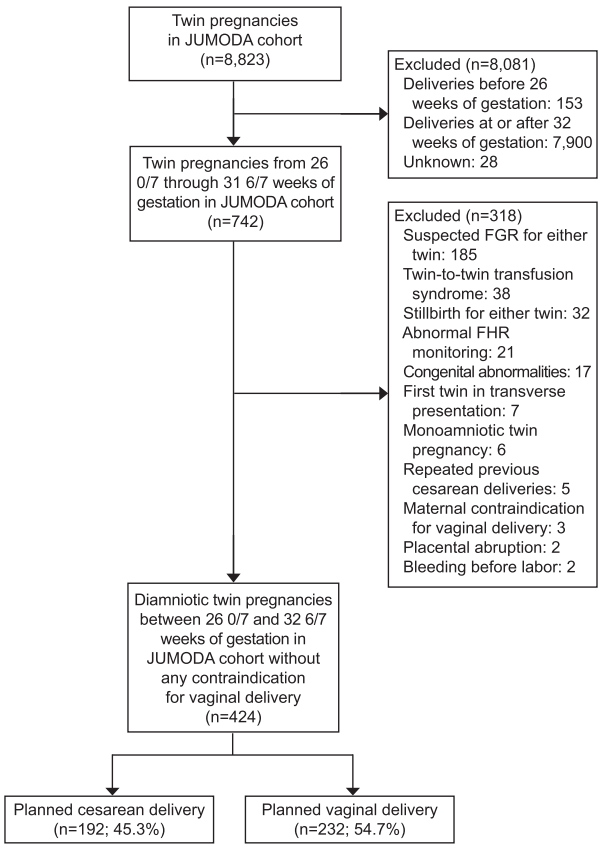

Fig. 1. Flowchart. JUMODA, JUmeaux MODe d'Accouchement; FGR, fetal growth restriction; FHR, fetal heart rate.

Korb. Planned Mode of Delivery for Very Preterm Twins. Obstet Gynecol 2022.

supplemental oxygen at a postnatal gestational age of 36 weeks. This primary outcome was treated as a binary variable.

Other reported neonatal outcomes were 5-minute Apgar score less than 4; birth trauma (humerus, femur or skull fracture; spinal cord injury; or brachial plexus palsy); subdural or intracerebral hemorrhage confirmed by ultrasonography, computed tomography, or magnetic resonance imaging; encephalopathy according to the Sarnat classification[13]; seizures on at least two occasions within 72 hours after birth; endotracheal ventilation within 72 hours after birth for at least 24 hours; and proven neonatal sepsis during neonatal hospitalization, defined as a positive blood culture or cerebrospinal fluid culture.

We first compared the characteristics of the women and their pregnancies, labors, hospitals, and neonates in the two groups, and we tested the differences with χ^2 or Fisher exact tests for categorical variables, and student or Wilcoxon rank sum tests for continuous variables, as appropriate. To assess the association between planned mode of delivery and survival to discharge without severe neonatal morbidity, while controlling for confounding factors, we used a multivariate Poisson regression model with a robust variance calculation method to estimate adjusted relative risks (aRR) and 95% CIs. Potential confounders were selected from the literature and included previous cesarean delivery, chorionicity, pregnancy complications (gestational hypertension, preeclampsia, insulin-treated gestational diabetes, and placenta previa), antenatal corticosteroids, first and second twin presentation, gestational age at delivery, birth weight below the 10th centile, and maternity unit level. All factors were considered categorical variables. Generalized estimating equations were applied to take the correlation between the first and second twin from the same pregnancy into account.

The proportion of women with missing data for any covariate was 0.7%. In view of this low level of missing data, we worked on complete cases and did not use multiple imputations.

To further control for indication bias related to confounding factors that might influence both the choice of the planned mode of delivery and the primary outcome, we used a propensity score approach. The propensity score was defined as the probability of a planned cesarean delivery based on covariates. This analysis followed a three-step process. First, a propensity score was estimated for all pregnancies by a logistic regression model with the planned mode of delivery as the dependent variable in relation to the baseline maternal, obstetric, neonatal, and maternity-unit characteristics (variables listed in Appendix 2, available online at http://links.lww.com/AOG/C526). Then, the inverse probability of treatment weighting based on estimated propensity scores was used to obtain a synthetic population in which planned mode of delivery was independent of measured baseline covariates, as confirmed by the balance of standardized differences. Imbalance was checked by propensity score distribution and the calculation of standardized mean differences before and after applying the inverse probability of treatment weighting (Appendix 2, http://links.lww.com/AOG/C526). Finally, the association of the planned mode of delivery with survival to discharge without severe neonatal morbidity was quantified by relative risk and 95% CI, estimated from a Poisson regression model, without further adjustment.

Association between planned mode of delivery and survival to discharge without severe neonatal morbidity also was assessed according to birth order (first or second twin).

A sensitivity analysis limited to spontaneous preterm births also was performed. Spontaneous preterm births were defined as births occurring after preterm labor or preterm prelabor rupture of membranes.

All tests were two-sided; $P<.05$ was considered significant. We used Stata 13.1.

The National Data Protection Authority (DR-2013-528), the consultative committee on the treatment of information on personal health data for research purposes (13–298), and the committee for the protection of people participating in biomedical research (PP-13-014) approved this study. Women had received information and provided oral informed consent to participate, as reported previously.[11]

RESULTS

During the study period, 742 women gave birth to twins from 26 0/7 through 31 6/7 weeks of gestation. After the application of the selection criteria, this analysis included 424 women, 232 (54.7%) with planned vaginal delivery and 192 (45.3%) with planned cesarean delivery (Fig. 1).

Maternal demographic characteristics were similar between the two groups (Table 1). Women with planned cesarean delivery, compared with those with planned vaginal delivery, had hypertensive pregnancy complications and diabetes more often, and both preterm prelabor rupture of membranes and preterm labor less often (Table 1). At delivery, women with planned cesarean delivery had first and second twins in noncephalic presentation more often than those with planned vaginal deliveries (Table 2).

In the planned vaginal delivery group, 191 (82.3%) women delivered both twins vaginally, 29 (12.5%) had a cesarean delivery for both twins, and 12 (5.2%) had a cesarean delivery for the second twin after the vaginal delivery of the first twin.

The main indication for planned cesarean delivery was prematurity (56/192, 29.2%) (Table 3). The main indications for cesarean delivery during labor in the planned vaginal group were nonreassuring fetal heart rates (12/41, 29.3%).

No intrapartum deaths occurred (Table 4). Rates of survival to discharge without severe neonatal morbidity did not differ between the planned cesarean delivery (308/384, 80.2%) and planned vaginal delivery groups (375/464, 80.8%; crude relative risk 0.99; 95% CI 0.91–1.15) (Table 4). After adjustment for potential confounders, planned cesarean delivery was not associated with higher survival at discharge without severe neonatal morbidity than planned vaginal delivery (aRR 1.02, 95% CI 0.93–1.11) (Table 4).

Similarly, after applying propensity scores and assigning inverse probability of treatment weighting, planned cesarean delivery, compared with planned vaginal delivery, was not associated with higher survival to discharge without severe neonatal morbidity (odds ratio 1.11, 95% CI 0.84–1.46). Bronchopulmonary dysplasia was the most frequent contributor to severe neonatal morbidity in both groups, without any significant difference between them.

Analyses by twin order found similar results. For the first twin (151/192 [78.7%] vs 194/232 [83.6%]; aRR 0.98; 95% CI 0.88–1.09), as for the second (157/192 [81.8%] vs 181/232 [78.0%]; aRR 1.10, 95% CI 0.98–1.24), planned mode of delivery was not associated with survival without severe neonatal morbidity (Appendix 3, available online at http://links.lww.com/AOG/C526). In the sensitivity analysis limited to spontaneous preterm births, planned cesarean delivery was not associated with higher survival at discharge without severe neonatal morbidity than planned vaginal delivery (189/240 [78.8%] vs 373/462 [80.4%]; aRR 1.00, 95% CI 0.90–1.11) (Appendix 4, available online at http://links.lww.com/AOG/C526).

DISCUSSION

In this prospective population-based study of very preterm twin pregnancies, the overall risk of survival to discharge without severe neonatal morbidity did not differ by the planned mode of delivery.

Previous large retrospective population-based studies have found higher neonatal morbidity after vaginal delivery, compared with cesarean delivery, for very preterm twins.[3,6] But these studies were limited by the lack of data concerning the intended mode of delivery, which prevented consideration of the conditions in which practitioners chose the planned delivery route. Moreover, other significant data, such as pregnancy complications and indications for cesarean delivery, were unavailable, although they can influence both neonatal outcomes and mode of delivery.

Our results are in accordance with more recent studies that report no difference in severe neonatal morbidity by planned mode of delivery.[7,14] These studies, however, had some methodologic limitations, including small sample sizes[7] and retrospective design[7] or retrospective classification of the planned mode of delivery.[14]

The JUMODA cohort, owing to its prospective population-based design providing valid information about the planned mode of delivery, decided before labor or at the onset on labor, and recorded in the database immediately after delivery by the attending

Table 1. Maternal and Pregnancy Characteristics by Planned Mode of Delivery in Women With Very Preterm Twin Pregnancies (N=424)

Characteristic	Planned Cesarean Delivery (n=192)	Planned Vaginal Delivery (n=232)	*P*
Age (y)			.21
Younger than 30	57 (29.7)	82 (35.3)	
30–39	83 (42.2)	103 (44.4)	
40 or older	52 (27.1)	47 (20.3)	
Geographic region of birth			.69
Europe	148 (88.1)	178 (86.0)	
North Africa	11 (6.6)	13 (6.3)	
Africa other	8 (4.8)	12 (5.8)	
Others	1 (0.6)	4 (1.9)	
Prepregnancy BMI (kg/m^2)			.85
Less than 18.5	16 (8.7)	16 (7.4)	
18.5–24.9	103 (56.0)	130 (59.9)	
25–29.9	44 (23.9)	46 (21.2)	
30 or higher	21 (11.4)	25 (11.5)	
Parity			.27
Nulliparous	126 (65.6)	141 (61.0)	
Multiparous without previous cesarean	46 (24.0)	71 (30.7)	
Multiparous with previous cesarean	20 (10.4)	19 (8.2)	
Smoking during pregnancy	32 (17.0)	40 (17.7)	.86
IVF, ICSI	58 (30.4)	62 (26.8)	.42
Chorionicity			.39
Dichorial	158 (82.3)	198 (85.3)	
Monochorionic diamniotic	34 (17.7)	34 (14.7)	
Pregnancy complications	49 (25.5)	22 (9.5)	<.001
Gestational hypertension	12 (6.3)	5 (2.2)	
Preeclampsia	29 (15.1)	3 (1.3)	
Insulin-treated gestational diabetes	8 (4.2)	14 (6.0)	
Placenta previa	8 (4.2)	0 (0.0)	
Preterm labor	114 (59.7)	175 (75.4)	<.001
PPROM twin 1 or twin 2	43 (22.5)	74 (32.0)	.03
Antenatal corticosteroids	173 (91.1)	200 (86.2)	.12

BMI, body mass index; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; PPROM, preterm prelabor rupture of membranes. Data are n (%) unless otherwise specified.

obstetricians and the substantial number of neonates included, strengthened the level and quality of the available evidence. In addition, the indication bias inherent in this design was taken into account by an appropriate statistical method.

On the other hand, our results differ from those of a population-based retrospective cohort study conducted in the Netherlands that reported that planned cesarean delivery was associated with significantly higher perinatal mortality and morbidity than planned vaginal delivery.[8] Nevertheless, the result this retrospective study should be interpreted with caution. First, it included neonatal events with heterogeneous degrees of severity, which raises questions about its definition of severe neonatal morbidity. Second, the planned cesarean delivery rate was much lower than in the JUMODA cohort, possibly due to misclassification of the planned mode of delivery inherent to its retrospective design from three different databases. Both of these differences may well influence the finding about the association between planned mode of delivery and neonatal morbidity.

When deciding on a planned mode of delivery, it is necessary to assess the mortality and morbidity in the neonatal period but also midterm and long-term outcomes. The EPIPAGE 2 study showed that survival at two years of corrected age without neurosensory impairment did not differ for very preterm twins between the planned vaginal and planned cesarean delivery groups.[14] The absence of benefits associated with planned cesarean delivery, compared with planned vaginal delivery, in both short-term and long-term infant outcomes suggests that very preterm delivery should not be considered a per se indication for planned cesarean in twin pregnancies.

Table 2. Labor, Delivery, and Neonatal Characteristics by Planned Mode of Delivery in Women With Very Preterm Twin Pregnancies (N=424)

Characteristic	Planned Cesarean Delivery (n=192)	Planned Vaginal Delivery (n=232)	*P*
Spontaneous onset of labor	120 (62.5)	231 (99.6)	<.001
Noncephalic 1st twin	84 (44.2)	32 (13.8)	<.001
Noncephalic 2nd twin	138 (71.9)	132 (56.9)	.001
Mode of delivery			<.001
Vaginal	2 (1.0)	191 (82.3)	
Cesarean	190 (99.0)	29 (12.5)	
Cesarean for 2nd twin	0 (0.0)	12 (5.2)	
Gestational age at birth (wk)			.17
26 0/7–27 6/7	46 (24.7)	50 (21.7)	
28 0/7–29 6/7	56 (30.1)	55 (23.9)	
30 0/7–31 6/7	84 (45.2)	125 (54.3)	
Birth weight (g)			
Twin 1	1,274±23	1,354±21	.01
Below 10th centile	31 (19.6)	32 (16.3)	.64
Twin 2	1,257±23	1,397±21	<.001
Below 10th centile	31 (19.6)	32 (16.3)	.64
No. of twin births per year			.30
Fewer than 50	22 (11.5)	23 (9.9)	
50–100	76 (39.6)	78 (33.6)	
100 or more	94 (49.0)	131 (56.5)	
University center	128 (66.7)	171 (73.7)	.11
Maternity level			.36
1	3 (1.6)	8 (3.5)	
2	21 (10.9)	20 (8.6)	
3	168 (87.5)	204 (87.9)	

Data are n (%) or mean±SD unless otherwise specified.

The likelihood that a randomized trial providing comparable groups for the two planned modes of delivery and circumventing indication bias is low, given the large number of pregnancies required to demonstrate a significant difference between groups in the specific context of preterm delivery. Indeed, two previous randomized trials aimed at comparing neonatal outcomes according to the planned mode of delivery for preterm breech and preterm vertex singletons were interrupted because of the inability

Table 3. Indications for Cesarean Delivery

Indication	Planned Cesarean Delivery (n=192)	Planned Vaginal Delivery (n=41)
Preterm birth	56 (29)	—
Breech presentation of 1st twin	40 (21)	—
Hypertensive pathologies	27 (14)	—
PROM	25 (13)	—
Chorioamnionitis	8 (4)	—
Other maternal cause	7 (4)	—
Antenatal bleeding	7 (4)	—
Noncephalic 2nd twin	5 (3)	—
Previous cesarean	3 (2)	—
Unfavorable cervix	2 (1)	—
Cesarean for the 2nd twin*	—	12 (29)
FHR abnormalities	—	12 (29)
Cord prolapse	—	6 (15)
Failure to progress	—	4 (10)
Other	4 (2)	5 (12)

PROM, prelabor rupture of membranes; FHR, fetal heart rate.
Data are n (%).
* Indications of cesarean for the second twin (n=12): cervical retraction (5), bradycardia (2), failure of maneuvers (2), arm prolapse (1), placental abruption (1), failure to progress (1).

Table 4. Neonatal Outcomes According to Planned Mode of Delivery for Very Preterm Twin Pregnancies (n=848)

Outcome	Planned Cesarean Delivery (n=384)	Planned Vaginal Delivery (n=464)	*P*	Crude RR (95% CI)	Adjusted RR (95% CI)*	RR (95% CI) After IPTW
Primary outcome						
Survival to discharge without severe neonatal morbidity†	308 (80.2)	375 (80.8)	.82	0.99 (0.91–1.08)	1.02 (0.93–1.11)	1.11 (0.84–1.46)
Secondary outcomes						
Death	12 (3.1)	5 (1.1)	.03			
Intrapartum	0	0				
Neonatal	12	5				
Severe neonatal morbidity						
Bronchopulmonary dysplasia	55 (14.3)	74 (16.0)	.51			
Intraventricular hemorrhage grade III–IV	7 (1.8)	9 (1.9)	.90			
Periventricular leukomalacia	7 (1.8)	4 (0.9)	.22			
Necrotizing enterocolitis grade 2 or higher	6 (1.6)	6 (1.3)	.74			
Other neonatal morbidity outcomes						
5-min Apgar score less than 4	11 (2.9)	9 (1.9)	.38			
Neonatal trauma	3 (0.8)	1 (0.2)	.23			
Long bone fracture	3	1				
Brachial plexus palsy	0	0				
Skull fracture	0	0				
Encephalopathy	0	1 (0.2)	—			
2 or more seizures within 72 h after birth	0	0	—			
Endotracheal tube after more than 24 h, within 72 h after birth	111 (28.9)	111 (23.9)	.10			
Proven neonatal sepsis	57 (14.8)	67 (14.4)	.87			

RR, relative risk; IPTW, inverse probability of treatment weighting.
Data are n (%) unless otherwise specified.
* Adjusted for previous cesarean, chorionicity, pathologies during pregnancy, antenatal corticosteroids, first and second twin presentation, gestational age, birth weight below the 10th centile, maternity unit level.
Results were estimated using a marginal model (generalized estimating equation) to take into account correlation between twins.
† Severe neonatal morbidity defined as any of the following: bronchopulmonary dysplasia, grade 3 or grade 4 intraventricular hemorrhage, periventricular leukomalacia, stage 2 or stage 3 necrotizing enterocolitis.

of the investigators to recruit women.[15–17] Consequently, the choice of the best mode of planned delivery for very preterm twins will continue to rely on the results of observational studies. Further population-based cohort studies could help to determine the subgroups in which one of the planned modes of delivery might improve short-term and long-term maternal and infant benefits.

The strengths of the JUMODA study include its population-based cohort design and prospective enrollment of all women giving birth in more than 95% of the maternity units that performed more than 1,500 deliveries annually in France in 2014 and the inclusion all level 3 maternity units in which very preterm births are supposed to occur. Inclusions for only one year limited bias linked to differences in obstetric practices and neonatal care over the study period. Attending obstetricians prospectively collected the data about planned mode of delivery and management of delivery so that thorough and accurate information was available for the variable of interest.

We took the bias inherent in this type of observational study into account, first by a rigorous selection of the population, with exclusion of pregnancy complications such as fetal growth restriction, which might have influenced both the choice of the planned mode of delivery and the primary outcome in one of the two groups (in particular, the planned cesarean delivery group) and by the sensitivity analysis considering only the spontaneous preterm births.

Second, we used diverse statistical approaches to adjust for confounding factors and a propensity score analysis to minimize the likelihood of incorrectly attributing any risk of neonatal morbidity to planned cesarean delivery.

Finally, with an 82% rate of successful planned vaginal delivery, this secondary analysis of the JUMODA cohort allowed analyzing the neonatal complications associated with very preterm vaginal delivery, the clinical situation often feared by practitioners.

The main limitation of our observational study is the possibility of uncontrolled confounders, which can persist despite the multiple statistical approaches used to reduce bias as much as possible.

Another limitation is the sample size, which limits our ability to reach statistical significance for small differences. Nonetheless, with a survival without severe neonatal morbidity rate of 80.8% in the planned vaginal delivery group as observed in this study, our analysis had a statistical power of 80% to show an absolute increase of 7% in this risk in the planned cesarean delivery group (we found a rate of 80.2% in this study). Therefore, we cannot formally exclude increases in neonatal survival associated with planned cesarean delivery lower than 7%. The sample size did not allow performing analyses according to fetal presentation. However, the fetal presentation was taken into account in the multivariate regression models.

Finally, our findings can be generalized only to centers where obstetricians are trained in and accustomed to vaginal deliveries for very preterm twins and to populations with comparable maternal characteristics.

Compared with planned vaginal delivery, planned cesarean delivery for very preterm twins is not associated with higher survival to discharge without severe neonatal morbidity. Very preterm delivery should not be considered a per se indication for planned cesarean in twin pregnancies. Practitioners should consider these results when informing women and deciding on the planned mode of delivery.

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