

OBSTETRICS

Association between gestational age and severe maternal morbidity and mortality of preterm cesarean delivery: a population-based cohort study



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BACKGROUND: Cesarean delivery rates at extreme prematurity have regularly increased over the past years, and few previous studies have investigated severe maternal morbidity associated with extreme preterm cesarean delivery.

OBJECTIVE: The aim of this study was to evaluate whether gestational age <26 weeks of gestation (weeks) was associated with severe maternal morbidity and mortality (SMMM) of preterm cesarean deliveries in comparison with cesarean deliveries between 26 and 34 weeks.

MATERIALS AND METHODS: The Etude Epidémiologique sur les petits âges gestationnels (EPIPAGE) 2 is a national prospective population-based cohort study of preterm births in 2011. We included mothers with cesarean deliveries between 22 and 34 weeks, excluding those who had a cesarean delivery for the second twin only and those with pregnancy terminations. SMMM was analyzed as a composite endpoint defined as the occurrence of at least 1 of the following complications: severe postpartum hemorrhage defined by the use of a blood transfusion, intensive care unit admission, or death. To assess the association of gestational age <26

weeks and SMMM, we used multivariate logistic regression and a propensity score—matching approach.

RESULTS: Among 2525 women having preterm cesarean deliveries, 116 before 26 weeks and 2409 between 26 and 34 weeks, 407 (14.4%) presented with SMMM. The SMMM occurred in 31 mothers (26.7%) who were at gestational age <26 weeks vs 376 (14.2%) between 26 and 34 weeks ($P < .001$). Cluster multivariate logistic regression showed significant association of gestational age <26 weeks and SMMM (adjusted odds ratio [aOR], 2.50; 95% confidence interval [CI], 1.42–4.40) and propensity score—matching analysis was consistent with these results (aOR, 2.27; 95% CI, 1.31–3.93).

CONCLUSION: Obstetricians should know about the higher SMMM associated with cesarean deliveries before 26 weeks, integrate this knowledge into decisions regarding cesarean delivery, and be prepared to manage the associated complications.

Key words: cesarean, extreme prematurity, prematurity, severe maternal morbidity

Management of preterm infants has greatly improved over the past years, with more and more active management provided for infants born at extreme gestational ages.^{1–5} Active antenatal care such as cesarean, in utero transfer and antenatal steroids initiated has been reported to be associated with improved neonatal survival before 26 weeks of gestation (weeks).^{6,7} In this context, cesarean rates at extreme prematurity have regularly increased these last few years.^{1–4} However, cohort studies of preterm infants reported variable rates of cesarean deliveries and

especially deliveries between 23 and 25 weeks, with noticeably lower rates for British (Population based studies of survival and later health status in extremely premature infants [EPICure 2])¹ and French (Etude Epidémiologique sur les Petits Ages Gestationnels 2 [EPIPAGE 2]) cohorts^{5,8} compared to American (*Eunice Kennedy Shriver* National Institute of Child Health and Human Development [NIHCHD])² and Swedish (Extremely Preterm Infants in Sweden Study, [EXPRESS]) cohorts.³ These heterogeneous care practices are observed across but also within countries, and can be related to reserved neonatal prognosis before 26 weeks and supposed maternal risks of cesarean deliveries at these extreme gestational ages.

Regardless of gestational age, an increase in the cesarean delivery rate has been reported as being associated with severe maternal morbidity and mortality (SMMM),⁹ but there is a paucity of data on SMMM of extreme preterm cesarean deliveries, particularly before 26 weeks. Operative complications of these cesarean

deliveries have been reported, with the use of a vertical incision in the upper uterine segment often needed^{10–12} and frequent difficulties with delivery because of fetal malpresentations and the not-yet-formed lower uterine segments. Therefore, we hypothesize that the risk of SMMM with cesarean delivery is higher before 26 weeks than for older gestational ages; however, a comparison with cesarean deliveries performed between 26 and 34 weeks has never been performed. Scientific societies recommend becoming knowledgeable about SMMM associated with these extreme preterm cesarean deliveries.¹³

The objective of this study was to investigate whether a gestational age of less than 26 weeks is an independent risk factor for SMMM associated with preterm cesarean delivery, by performing a secondary analysis of the national population-based cohort of preterm infants in EPIPAGE 2.⁴

Materials and Methods

Ethical approval

This study was approved by the National Data Protection Authority

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AJOG at a Glance

Why this study was conducted?

Severe maternal morbidity of preterm cesarean before 26 weeks of gestation is more than twice as high as that between 26 and 34 weeks. Cesarean delivery rates at extreme prematurity have regularly increased over the past years, and only a few studies have investigated severe maternal morbidity associated with extreme preterm cesarean delivery.

Key findings

The rate of severe maternal morbidity was twice as high with cesarean delivery before 26 weeks vs that between 26 and 34 weeks.

What does this add to what is known?

Obstetricians should be aware of the maternal risk of cesarean delivery at extreme prematurity, integrate it into decisions regarding cesarean delivery, and be prepared to manage the associated complications.

(CNIL no.911009), the Consultative Committee on the Treatment of Data on Personal Health for Research Purposes (reference no. 10.626), and the Committee for the Protection of People Participating in Biomedical Research (reference CPP SC-2873).

Study population and setting

The Etude Epidémiologique sur les Petits Ages Gestationnels 2 (EPIPAGE-2) is a prospective national population-based cohort study of preterm infants born between 22 and 34 completed weeks of gestational age in France in 2011 (all French regions except 1) including pregnancy terminations, stillbirths, and live births.⁴ Obstetric and postpartum data of mothers were also collected. Infants born at gestational ages of 22–26 weeks, 27–31 weeks, and 32–34 weeks were recruited for 8 months, 6 months, and 5 weeks respectively.⁴ Details about the design and methods have been published elsewhere.⁸ The Committee for the Protection of People Participating in Biomedical Research (CPP; March 18, 2011, ref SC-2873) approved this study.

For this analysis, we included all mothers of preterm infants born by cesarean delivery between 22 and 34 weeks of gestation enrolled in the EPIPAGE 2 cohort, excluding mothers giving birth to twins having a cesarean delivery only for the second twin and women with pregnancy terminations.

Data collection

Families received information and agreed to participate in the study prior to data collection. A coordinating committee was set up in each region specifically for the implementation of the study. Staff members were selected in each maternity ward and each neonatal unit to supervise inclusions and data collection. During recruitment, members of the regional coordinating committee visited all maternity units to ensure that all eligible children were identified. Data were collected on specific questionnaires at birth and during neonatal hospitalization extracted from medical records kept in 278 maternity units. Data extracted from maternity and neonatal records were entered directly online, with a secure interface to maintain the confidentiality and privacy of data and personal information. The EPIPAGE-2 coordination team used a centralized system to monitor and to validate inclusions and data collection at the national level.

Outcome and other studied factors

Severe maternal morbidity and mortality (SMMM) was analyzed as a composite endpoint defined as the occurrence of 1 of the following complications: severe postpartum hemorrhage defined by the use of a blood transfusion; intensive care unit (ICU) admission; or death.

The main factor studied was gestational age at cesarean delivery, classified as <26 weeks or \geq 26 weeks. The threshold of 26 weeks was chosen because of clinical relevance, given the frequent occurrence of technical difficulties for cesarean deliveries before 26 weeks.¹¹ Gestational age was the best estimate based on the date of the last menstrual period and an early prenatal ultrasonogram.

The other factors studied were as follows: maternal age, type of pregnancy (singleton or multiple), parity and scarred uterus, active smoking, pregestational diabetes, hospitalization for hypertension, type of prematurity (spontaneous or induced), type of anesthesia, maternal indication for cesarean delivery, and level of maternity units as defined in France since 1998 (level III facility before 33 weeks, level II facility between 33 and 36 weeks, level II A facility with neonatal unit and level II B with neonatal intensive care unit, and level I without a neonatal department).

Statistical analysis

We first described and compared maternal and maternity unit characteristics by gestational age <26 weeks or \geq 26 weeks and then by SMMM. Categorical variables were compared with the χ^2 test or Fisher exact test as appropriate. For continuous variables, data were analyzed with *t* tests and Wilcoxon tests as appropriate. To account for the inclusion scheme of the study and for representative preterm birth in France, a weighted coefficient was calculated according to the length of the inclusion period and allocated to each individual (1 for births between 22 and 26 weeks, 1.346 for births between 27 and 31 weeks, and 7 for births between 32 and 34 weeks).

The main analysis was then performed, which consisted of a multivariate logistic regression model to quantify the association between gestational age with the threshold of 26 weeks and SMMM with adjusted odds ratios (aOR) and 95% confidence intervals (95% CI). The variables included in the multivariate model were gestational age with the threshold of 26 weeks, variables chosen according to their clinical relevance, and

variables with a P value of $<.20$ in the univariate analysis.

To take into account a potential center effect (278 maternity units), the analysis included the cluster design of the data. A sensitivity analysis was then performed with the same variables and with gestational age according to 3 modalities (<26 weeks, 26–31 weeks, and ≥ 32 weeks).

As a secondary analysis, to control for potential indication bias, we used a propensity score–matching approach (method optimal, ratio 1:10) to check for baseline confounding factors that might influence either SMMM or delivery before 26 weeks. The propensity score was based on the following baseline factors: maternal age, type of pregnancy (singleton vs multiple), parity and scarred uterus, active smoking, pregestational diabetes, hospitalization for hypertension (only 1 variable used to evaluate hypertensive pathology to avoid overadjustment and to limit measurement bias), type of prematurity (spontaneous or induced) and maternal indication for cesarean delivery. The propensity score considered gestational age (<26 weeks vs ≥ 26 weeks) as a

dependent variable and was defined as the probability that the cesarean delivery would have been performed at an extreme preterm gestational age depending on woman's baseline characteristics.¹⁴ A model was then proposed on the matched sample with SMMM as a dependent variable, gestational age (<26 weeks vs ≥ 26 weeks) as the primary exposure of interest, and general anesthesia (postbaseline factor associated with the act of cesarean delivery) as an independent variable. There were no missing data for gestational age, maternal age, type of pregnancy, scarred uterus, and type of maternity unit. Missing data were not specifically addressed because they corresponded to less than 5% of data.

Data were analyzed using R Studio V.1.0.44 and survey package for the specific design of the study. Statistical significance was set at 2-tailed $P < .05$.

Results

Population, maternity units, and cesarean delivery rates

Among the 4620 mothers included in EIPAGE 2 study, 2548 (56.2%) had

cesarean deliveries between March and December 2011.

Our study included 2525 mothers (Figure 1) after the exclusion of 23 mothers who had a cesarean delivery only for the second twin: 116 (16.0%) between 22 and 25 weeks, 429 (63.6%) between 26 and 27 weeks, 1456 (69.8%) between 28 and 31 weeks, and 524 (54.2%) between 32 and 34 weeks.

Among the 2525 mothers, 116 (4.6%) had a cesarean delivery before 26 weeks and 2409 (95.4%) between 26 and 34 weeks.

SMMM occurred in 407 (14.4%) cases: 77 mothers had severe postpartum hemorrhage, 369 were admitted to ICU, and 1 died 41 days after delivery (after liver transplantation because of fulminant hepatitis B).

The SMMM rate among the vulnerable gestational ages were 50% at 22 weeks, 25% at 23 weeks, 21.7% at 24 weeks, and 27% at 25 weeks.

The main characteristics of the study population are presented in Table 1.

Gestational age <26 weeks was significantly associated with SMMM, general anesthesia, and type III of maternity units, whereas pre-gestational diabetes, hospitalization for hypertension, and induced prematurity were associated with cesarean deliveries between 26 and 34 weeks.

The main indications for cesarean deliveries before 26 weeks were as follows: systematic because of the gestational age (obstetric decision based only on prematurity), fetal presentation, or multiple pregnancy in 29 cases (27.9%); non-reassuring fetal heart rate in 9 (8.6%); arrest of labor in 2 (1.9%); fetal pathology in 7 (6.7%); maternal pathology in 27 (26.0%); and (vi) other factors in 30 (28.8%).

The main indications for cesarean deliveries between 26 and 34 weeks were as follows: systematic because of gestational age, fetal presentation, or multiple pregnancy in 315 cases (12.5%); non-reassuring fetal heart rate in 397 (18.5%); arrest of labor in 30 (1.8%); fetal pathology in 385 (17.4%); maternal pathology in 696 (26.0%); and other factors in 389 (32.5%). The most common maternal indications for preterm

FIGURE 1
Flow chart of the study population

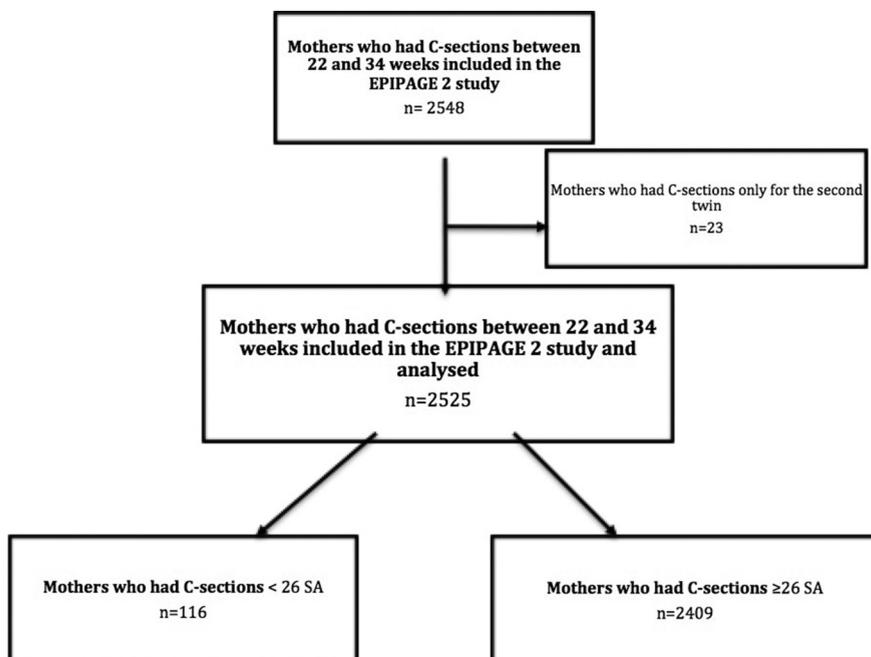


TABLE 1
Maternal and unit characteristics by gestational age

Principal characteristics	<26 wk n = 116	≥26 wk n = 2409	<i>P</i>
Maternal age, y, n = 2525	29.4 ± 6.0	30.5 ± 5.8	.06
Type of pregnancy, n = 2525			
Singleton	91 (78.5)	1921 (78.2)	.94
Multiple	25 (21.5)	488 (21.8)	
Parity and scarred uterus, n = 2499			
Parity = 0	67 (57.7)	1218 (51.7)	.11
Parity ≥1 and no uterine scar	25 (18.1)	753 (30.9)	
Parity ≥1 and uterine scar	24 (24.1)	412 (17.4)	
Active smoking, n = 2427	17 (15.7)	528 (21.4)	.17
Pregestational diabetes, n = 2495	0	54 (2.7)	<.001
Hospitalization for hypertension, n = 2477	22 (19.5)	727 (29.1)	.03
Prematurity, n = 2407			
Spontaneous	41 (36.0)	455 (19.1)	<.001
Induced	73 (64.0)	1838 (80.9)	
General anesthesia, n = 2365	45 (41.3)	469 (18.6)	<.001
Type of uterine incision, n = 1978			
Classical incision	30 (34.9)	228 (7.8)	<.001
Low transverse incision	56 (56.1)	1664 (92.2)	
Maternal indication for cesarean delivery, n = 2215	33 (31.7)	881 (41.7)	.05
Type of maternity unit, n = 2525			
I	5 (4.3)	72 (3.6)	<.001
II A	3 (2.6)	165 (12.1)	
II B	7 (6.0)	249 (17.6)	
III	101 (87.1)	1923 (66.8)	
SMMM, n = 2525	31 (26.7)	376 (14.2)	<.001
Blood transfusion, n = 2525	10 (8.6)	67 (2.2)	<.001
ICU admission, n = 2525	23 (19.8)	346 (13.1)	.05
Death, n = 2525	0	1	<.001

ICU, intensive care unit; SMMM, severe maternal morbidity and mortality.

Data are n (%) or mean ± standard deviations, all proportions are weighted according to differential recruitment.

Boldface type indicates significance ($P < .05$).

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cesareans were preeclampsia, eclampsia, HELLP syndrome, diabetes, and placenta previa.

Fetal presentation was breech in 57 cases (53.3%) before 26 weeks and in 723 (27.8%) between 26 and 34 weeks. Other presentations such as transverse lie occurred in 11 cases (10.3%) before 26 weeks and in 135 cases (5.7%) between

26 and 34 weeks ($P < .001$). Difficulties in delivery occurred in 10 cases (10.9%) before 26 weeks vs 110 (4.7%) between 26 and 34 weeks ($P = .07$).

Univariate and multivariate cluster analysis

The following factors were associated with SMMM: gestational age before 26

weeks ($P < .001$), hospitalization for hypertension ($P < .001$), induced prematurity ($P < .01$), general anesthesia ($P < .001$), and maternal indication for cesarean delivery ($P < .001$). No significant association was found between type of uterine incision and SMMM ($P = .77$).

After the multivariate cluster analysis, mothers having a cesarean delivery before 26 weeks presented with more than a 2-fold increase in the risk of SMMM compared with those having a cesarean delivery between 26 and 34 weeks (Tables 2 and 3) (adjusted odds ratio [aOR], 2.50; 95% confidence interval [CI], 1.42–4.44, $P = 0.001$).

The other variables statistically associated with SMMM were pregestational diabetes (aOR, 2.64; 95% CI, 1.02–6.60), hospitalization for hypertension (aOR, 2.66; 95% CI, 1.83–3.85), general anesthesia (aOR, 3.41; 95% CI, 2.37–4.91), and maternal indication for cesarean (aOR, 2.22; 95% CI, 1.44–3.43). The other variables included in the multivariate analysis were type of pregnancy (singleton vs multiple), parity and scarred uterus, active smoking, and prematurity (spontaneous vs induced).

Considering gestational age according to 3 modalities showed consistent results ($P = .007$); in comparison with the reference group of gestational age between 32 and 34 weeks, gestational age <26 weeks was significantly associated with SMMM (aOR 2.50; 95% CI, 1.41–4.45; $P = .002$), but no significant association between gestational age between 26 and 31 weeks and SMMM was found (aOR, 1.03; 95% CI, 0.68–1.56, $P = .89$).

Propensity score – matching approach

The results of this secondary analysis based on propensity score matching were consistent with the previous results: gestational age <26 weeks was significantly associated with SMMM in 2 different models adjusted for a potential confounding factor related (aOR, 2.27; 95% CI, 1.31–3.93) or not related (aOR, 3.11; 95% CI, 1.84–5.25) to cesarean delivery (general anesthesia).

Comment

From a national population-based cohort study, we showed that mothers undergoing a cesarean delivery before 26 weeks had more than a 2-fold increase in the risk of SMMM compared with those undergoing a cesarean delivery between 26 and 34 weeks.

The comparison of outcomes of cesarean deliveries before 26 weeks vs between 26 and 34 weeks has not been evaluated in the literature, but appears to be more clinically relevant than a comparison with term cesarean deliveries. The threshold of 26 weeks was chosen because of reported operative complications of these cesarean deliveries with the frequent need for a vertical incision in the upper uterine segment and frequent operative difficulties related to fetal malpresentations and the not-yet-formed lower uterine segment for these preterm births.^{10,15–18} Classical incision on the upper segment has been known to represent a higher risk of maternal complications (infections, hemorrhage, blood transfusion and ICU admission).^{16,18–21}

To our knowledge, our study is the first to report this design analyzing SMMM of only cesarean deliveries at extreme prematurity and to specifically investigate the association between gestational age and maternal morbidity. In fact, a higher rate of maternal mortality related to cesarean compared to vaginal delivery is established regardless of the gestational age^{22–25} and an association between prematurity and maternal morbidity has been reported regardless of the mode of delivery and may be related to an indication bias.^{11,24–26}

The strength of our study includes the specific prospective population-based cohort design,⁴ in contrast to underpowered retrospective studies.²⁷ The number of mothers who had preterm cesarean deliveries before 26 weeks ensured enough power to address our initial hypothesis.

The external validity is high because EPIPAGE2 is a nationwide study and because cluster analysis took into account a potential center effect. It would be interesting to study SMMM in

TABLE 2

Association of maternal and unit characteristics with severe maternal morbidity and mortality

Variables	Univariate analysis		
	SMMM group n = 407	No-SMMM group n = 2118	P
Gestational age			
≥26 wk	376 (92.4)	2033 (96.0)	<.001
<26 wk	31 (7.6)	85 (4.0)	
Maternal age, y	30.6 ± 5.9	30.4 ± 5.8	.73
Type of pregnancy			
Singleton	338 (83.0)	1674 (79.0)	.25
Multiple	69 (17.0)	444 (21.0)	
Parity and scarred uterus			
Parity = 0	199 (49.5)	1086 (51.8)	.18
Parity ≥1 and no uterine scar	137 (34.1)	641 (30.6)	
Parity ≥1 and uterine scar	66 (16.4)	370 (17.6)	
Active smoking	67 (16.5)	478 (22.6)	.13
Pregestational diabetes	11 (2.7)	43 (2.0)	.18
Hospitalization for hypertension	200 (49.1)	549 (25.9)	<.001
Placenta previa	30 (6.7)	120 (8.0)	.50
Prematurity			
Spontaneous	49 (12.1)	459 (21.8)	<.01
Induced	357 (87.9)	1644 (78.2)	
General anesthesia	142 (36.6)	372 (18.8)	<.001
Type of uterine incision			
Classical incision	46 (8.7)	212 (8.2)	.77
Low transverse incision	284 (91.3)	1436 (91.8)	
Maternal indication for cesarean delivery	249 (67.8)	665 (36.0)	<.001
Preeclampsia	189 (50.9)	385 (20.8)	<.001
Eclampsia	18 (5.0)	17 (0.5)	.005
HELLP syndrome	85 (22.4)	108 (5.8)	<.001
Diabetes	10 (3.7)	55 (4.3)	0.71
Placenta previa	30 (6.7)	120 (8.0)	0.50
Type of maternity unit			
I	8 (2.4)	69 (3.8)	0.17
IIA	20 (8.0)	148 (12.5)	
IIB	43 (15.7)	213 (17.7)	
III	336 (73.9)	1688 (66.0)	

SMMM, severe maternal morbidity and mortality.

Data are n (%) or mean ± standard deviation; all proportions are weighted according to differential recruitment.

Boldface type indicates significance ($P < .05$).

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TABLE 3
Association between severe maternal morbidity and maternal characteristics

Variables	Cluster multivariate analysis
	aOR (95% CI)
Maternal age, y	0.99 (0.96–1.02)
Type of pregnancy	
Singleton	1
Multiple	1.62 (0.86–3.07)
Parity and scarred uterus	
Parity = 0	1
Parity ≥1 and no uterine scar	1.14 (0.79–1.65)
Parity ≥1 and uterine scar	0.62 (0.38–1.01)
Gestational age	
≥26 SA	1
<26 SA	2.50 (1.42–4.40)
Active smoking	0.87 (0.48–1.59)
Pregestational diabetes	2.64 (1.02–6.60)
Hospitalization for hypertension	2.66 (1.83–3.85)
Prematurity	
Spontaneous	1
Induced	0.96 (0.54–1.69)
General anesthesia	3.41 (2.37–4.91)
Maternal indication for cesarean delivery	2.22 (1.44–3.43)

aOR, adjusted odds ratio (adjusted for maternal age, type of pregnancy, parity and scarred uterus, gestational age, active smoking, pregestational diabetes, hospitalization for hypertension, type of prematurity, general anesthesia, and maternal indication for cesarean delivery; CI, confidence interval).

Boldface type indicates significance ($P < .05$).

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American and Swedish cohorts with high proportions of cesarean deliveries before 26 weeks.

Multiple pregnancy, which has a high incidence in the population of preterm deliveries, could be a confounding factor potentially associated with our primary exposure of interest (gestational age <26 weeks) and our main outcome (SMMM). This factor was taken into account in our study, by including it in the cluster multivariate analysis and in the propensity score–matching approach. Therefore, our population of analysis should be close to the target population.

The originality of our study is the use of different statistical strategies to limit indication bias that could affect

maternal outcomes. The propensity score–matching approach was used to check for confounding factors that might influence either SMMM or delivery before 26 weeks. This strategy confirmed the association between SMMM and the operative act of cesarean delivery, regardless of prior maternal morbidity. Furthermore, gestational age <26 weeks is an independent factor for SMMM associated with cesarean deliveries, whatever the type of maternal indication (preeclampsia, eclampsia, HELLP syndrome, diabetes, placenta previa; data not provided because of a large proportion of missing data). This leads us to believe that SMMM associated with cesarean deliveries before 26 weeks is related to preoperative maternal

morbidity of these mothers but also to operative difficulties of these cesarean deliveries. SMMM should be associated with the incision on a preterm uterus, whatever the type of incision. Furthermore, SMMM was associated with gestational age <26 weeks, regardless of whether the prematurity was spontaneous or induced. Before deciding on a cesarean delivery, it therefore seems important to have shared decision making and to weigh maternal morbidity, neonatal morbidity, and survival at these vulnerable gestational ages and particularly at periviable ages. Perlberg et al reported that only 31% of infants were alive at discharge at 24 weeks and 60% at 25 weeks during the same period.⁵ This information is especially needed in case of spontaneous prematurity when spontaneous vaginal delivery is feasible. A recent study reported a significant association between maternal complications and spontaneous periviable birth regardless mode of delivery.²⁶ As recommended in the consensus report on obstetric care for periviable birth, decisions should include declining or accepting interventions and therapies based on individual circumstances and individual values.²⁸

One of the limitations of our study was the evaluation of SMMM. The definition of SMMM is not standardized in the literature and is sometimes defined as blood transfusion and/or hysterectomy to define severe postpartum hemorrhage, ICU admission, death, and length of hospitalization exceeding 7 days.²⁹ Other authors have defined SMMM as the occurrence of an infection, surgical injury, endometritis, readmission,^{11,30} or reopening or unexpected procedure.¹¹ In our study, severe postpartum hemorrhage was defined by the need for blood transfusion and not by estimated blood loss, initial hematocrit averages, or hysterectomy (which were not available in our data), and data were collected before a core outcome set was developed and published.³¹ Furthermore, we did not choose maternal hospital stays exceeding 7 days because the length of stay could be related to neonatal hospitalization.

Another limitation was the evaluation of the severity of the pathology of women hospitalized for hypertension before cesarean delivery, because the variable “hospitalization for hypertension” was chosen. Other variables (HELLP syndrome, eclampsia) were not chosen to evaluate hypertensive pathology to avoid overadjustment, to limit measurement bias, and because these variables presented more missing data than “hospitalization for hypertension.”

We reported SMMM in 14.4% of cases in our cohort, which is substantial and more specific than prior studies describing 8.6% of serious complications regardless of the mode of delivery.¹¹ Before 26 weeks, SMMM risk was more than twice as frequent as between 26 and 34 weeks; and because 20% of mothers had cesarean deliveries in type I and II maternity units, all practitioners must be aware of the potential complications of preterm cesarean deliveries and be prepared to manage them. Developing and implementing optimal management of these patients along with training of practitioners are therefore needed because preterm cesarean deliveries will never be performed exclusively in type III maternity units.

Only a few studies, with low levels of evidence (because of small samples, retrospective cohorts, and case-control studies), have investigated outcomes of subsequent pregnancies after preterm cesarean delivery.^{32–34} The risks of uterine rupture, previa placenta, and/or accreta, postpartum hemorrhage, hysterectomy, maternal death, or in utero death were documented, but gestational age of index cases of cesarean deliveries has not been confirmed to be an associated factor. Other studies are therefore needed to answer this question.

In conclusion, our study showed that gestational age <26 weeks was an independent risk factor for SMMM in cases of preterm cesarean deliveries. These results should encourage reflection on obstetric management of these women by practitioners from all categories of maternity ward, along with shared decision making.

Other studies are required to evaluate mid- and long-term morbidity and

outcomes of subsequent pregnancies after these preterm cesarean deliveries. ■

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References

- Costeloe KL, Hennessy EM, Haider S, Stacey F, Marlow N, Draper ES. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). *BMJ* 2012;345:e7976.
- Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics* 2010;126:443–56.
- EXPRESS Group, Fellman V, Hellström-Westas L, et al. One-year survival of extremely preterm infants after active perinatal care in Sweden. *JAMA* 2009;301:2225–33.
- Ancel P-Y, Goffinet F; EPIPAGE 2 Writing Group. EPIPAGE 2: a preterm birth cohort in France in 2011. *BMC Pediatr* 2014;14:97.
- Perlbarg J, Ancel PY, Khoshnood B, et al. Delivery room management of extremely preterm infants: the EPIPAGE-2 study. *Arch Dis Child Fetal Neonatal Ed* 2016;101:F384–90.
- Draper ES, Zeitlin J, Fenton AC, et al. Investigating the variations in survival rates for very preterm infants in 10 European regions: the MOSAIC birth cohort. *Arch Dis Child Fetal Neonatal Ed* 2009;94:F158–63.
- Diguisto C, Goffinet F, Lorthe E, et al. Providing active antenatal care depends on the place of birth for extremely preterm births: the EPIPAGE 2 cohort study. *Arch Dis Child Fetal Neonatal Ed* 2017;102:F476–82.
- Ancel P-Y, Goffinet F, EPIPAGE-2 Writing Group, et al. Survival and morbidity of preterm children born at 22 through 34 weeks' gestation in France in 2011: results of the EPIPAGE-2 cohort study. *JAMA Pediatr* 2015;169:230–8.
- Villar J, Valladares E, Wojdyla D, et al. Caesarean delivery rates and pregnancy outcomes: the 2005 WHO global survey on maternal and perinatal health in Latin America. *Lancet* 2006;367:1819–29.
- Bethune M, Permezel M. The relationship between gestational age and the incidence of classical caesarean section. *Aust N Z J Obstet Gynaecol* 1997;37:153–5.
- Reddy UM, Rice MM, Grobman WA, et al. Serious maternal complications after early preterm delivery (24–33 weeks' gestation). *Am J Obstet Gynecol* 2015;213:538.
- Baeza C, Mottet N, Coppola C, Desmarests M, Ramanah R, Riethmuller D. [Obstetrical prognosis of patients after a previous caesarean section performed before 32 weeks of amenorrhoea]. *Gynecol Obstet Fertil* 2016;44:629–35.
- Raju TN, Mercer BM, Burchfield DJ, Joseph GF Jr. Periviable birth: executive summary of a joint workshop by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, American Academy of Pediatrics, and American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2014;123:1083–96.
- D'Agostino RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998;17:2265–81.
- Greene RA, Fitzpatrick C, Turner MJ. What are the maternal implications of a classical caesarean section? *J Obstet Gynaecol J Inst Obstet Gynaecol* 1998;18:345–7.
- Lao TT, Halpern SH, Crosby ET, Huh C. Uterine incision and maternal blood loss in preterm caesarean section. *Arch Gynecol Obstet* 1993;252:113–7.
- Luthra G, Gawade P, Starikov R, Markenson G. Uterine incision-to-delivery interval and perinatal outcomes in transverse versus vertical incisions in preterm caesarean deliveries. *J Matern-Fetal Neonatal Med* 2013;26:1788–91.
- Patterson LS, O'Connell CM, Baskett TF. Maternal and perinatal morbidity associated with classic and inverted T caesarean incisions. *Obstet Gynecol* 2002;100:633–7.
- Shah YG, Ronner W, Eckl CJ, Stinson SK. Acute maternal morbidity following classical caesarean delivery of the preterm infant. *Obstet Gynecol* 1990;76:16–9.
- Blanco JD, Gibbs RS. Infections following classical caesarean section. *Obstet Gynecol* 1980;55:167–9.
- Halperin ME, Moore DC, Hannah WJ. Classical versus low-segment transverse incision for preterm caesarean section: maternal complications and outcome of subsequent pregnancies. *Br J Obstet Gynaecol* 1988;95:990–6.
- Hall MH, Bewley S. Maternal mortality and mode of delivery. *Lancet* 1999;354:776.
- Esteves-Pereira AP, Deneux-Tharaux C, Nakamura-Pereira M, Saucedo M, Bouvier-Colle M-H, Leal M do C. Caesarean delivery and postpartum maternal mortality: a population-based case control study in Brazil. *PLoS One* 2016;11:e0153396.
- Deneux-Tharaux C, Carmona E, Bouvier-Colle M-H, Bréart G. Postpartum maternal mortality and caesarean delivery. *Obstet Gynecol* 2006;108:541–8.
- Kilpatrick SJ, Abreo A, Gould J, Greene N, Main EK. Confirmed severe maternal morbidity is associated with high rate of preterm delivery. *Am J Obstet Gynecol* 2016;215:233.
- Rossi RM, DeFranco EA. Maternal complications associated with periviable birth. *Obstet Gynecol* 2018;132:107–14.
- Bertholdt C, Menard S, Delorme P, Lamau M-C, Goffinet F, Le Ray C. Intraoperative adverse events associated with extremely preterm cesarean deliveries. *Acta Obstet Gynecol Scand* 2018;97:608–14.
- American College of Obstetricians and Gynecologists; Society for Maternal-Fetal Medicine. Obstetric care consensus no. 6: Periviable birth. *Obstet Gynecol* 2017;130:e187–99.
- Villar J, Carroli G, Zavaleta N, et al. Maternal and neonatal individual risks and benefits associated with caesarean delivery: multicentre prospective study. *BMJ* 2007;335:1025.
- Thomas PE, Petersen SG, Gibbons K. The influence of mode of birth on neonatal survival and maternal outcomes at extreme prematurity: a retrospective cohort study. *Aust N Z J Obstet Gynaecol* 2016;56:60–8.
- Schaap T, Bloemenkamp K, Deneux-Tharaux C, et al. Defining definitions: a Delphi study to develop a core outcome set for conditions of severe maternal morbidity. *Br J Obstet Gynecol* 2019;126:394–401.
- Eslier M, Lemonnier M, Koné M, Roumieux S, Dreyfus M. [Obstetrical outcome after a caesarean section before 28 weeks of gestation—a case-control study]. *J Obstet Biol Reprod (Paris)* 2016;45:1144–50.
- Maisonneuve A-S, Haumonte J-B, Carcopino X, et al. [Obstetrical outcome and risk of uterine rupture following a caesarean section before 32 weeks]. *J Gynecol Obstet Biol Reprod (Paris)* 2011;40:334–9.
- Kwee A, Smink M, Van Der Laar R, Bruinse HW. Outcome of subsequent delivery after a previous early preterm caesarean section. *J Matern-Fetal Neonatal Med* 2007;20:33–7.

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