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

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1 **Title page:**

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

4

5 **Authors:**

6 Julie BLANC^{1,2}, MD, Noémie RESSEGUIER², MD, François GOFFINET^{3,4}, MD, PhD, Elsa
7 LORTHE^{3,5}, RM, PhD, Gilles KAYEM^{3,6}, MD, PhD, Pierre DELORME^{3,4}, MD, Christophe
8 VAYSSIERE^{7,8}, MD, PhD, Pascal AUQUIER², MD, PhD, Claude D'ERCOLE^{1,2}, MD, PhD

9 **Affiliations**

10 1 Department of Obstetrics and Gynecology, Nord Hospital, APHM, chemin des Bourrely,
11 13015 Marseille, France

12 2 EA 3279, Public Health, Chronic Diseases and Quality of Life, Research Unit, Aix-
13 Marseille University, 13284 Marseille, France

14 3 Inserm UMR 1153, Obstetrical, Perinatal and Pediatric Epidemiology Research Team
15 (EPOPé), Research Center for Epidemiology and BioStatistics Sorbonne Paris Cité (CRESS),
16 Paris Descartes University, Paris, France

17 4 Maternité Port-Royal, University Paris-Descartes, DHU Risk in Pregnancy, Hôpitaux
18 Universitaires Paris Centre, Assistance Publique-Hôpitaux de Paris, Paris, France

19 5 EPIUnit – Institute of Public Health, University of Porto, Porto, Portugal

20 6 Department of Obstetrics and Gynecology, Trousseau University Hospital, Assistance
21 Publique-Hôpitaux de Paris, Sorbonne Universités, Université Pierre and Marie Curie Paris
22 06, 4 Place Jussieu, 75252 Paris cedex 05, Paris, France

23 7 Department of Obstetrics and Gynecology, Paule de Viguiet Hospital, CHU Toulouse,
24 Toulouse, France.

25 8 UMR 1027 INSERM, University of Paul Sabatier Toulouse III, Toulouse, France

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40

41 **Corresponding author:**

42 Julie Blanc, MD,

43 Department of Obstetrics and Gynecology, Nord Hospital, APHM, chemin des Bourrely,

44 13015 Marseille, France

45 EA 3279, Public Health, Chronic Diseases and Quality of Life, Research Unit, Aix-Marseille

46 University, 13284 Marseille, France

47 +33 491964672, fax number +33 491964696

48 julievirginie.blanc@ap-hm.fr

49

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51 **Condensation:**

52

53 Obstetricians should know about the higher Severe Maternal Morbidity and Mortality of
54 cesarean before 26 weeks, integrate it into the decision for cesarean and be trained to manage
55 these complications.

56

57 **Short title:**

58 Extreme preterm cesarean and severe maternal morbidity

59

60 **AJOG at a Glance:**

61 Severe maternal morbidity of preterm cesarean before 26 weeks of gestation is more than
62 twice as high as between 26 and 34 weeks.

63 **A. Why this study was conducted?**

64 Cesarean rates at extreme prematurity have regularly increased over the last years and few
65 previous studies investigated severe maternal morbidity of extreme preterm cesarean

66 **B. What are the key findings?**

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

69 **C. What does this study add to what is already known?**

70 Obstetricians should be aware of the maternal risk of cesarean at extreme prematurity,
71 integrate it into the decision of cesarean delivery and be prepared to manage these
72 complications.

73

74

75

76 **ABSTRACT:**

77 **Background:** Cesarean delivery rates at extreme prematurity have regularly increased over
78 the last years and few previous studies investigated severe maternal morbidity of extreme
79 preterm cesarean.

80 **Objective:** To evaluate if gestational age < 26 weeks of gestation (weeks) is associated with
81 severe maternal morbidity and mortality (SMMM) of preterm cesarean in comparison with
82 cesarean between 26 and 34 weeks.

83 **Study design:** The “Etude Epidémiologique sur les petits âges gestationnels” (EPIPAGE) 2 is
84 a national prospective population-based cohort study of preterm births in 2011. We included
85 mothers with cesareans between 22 and 34 weeks excluding those who had a cesarean for the
86 second twin only and pregnancy terminations. SMMM was analyzed as a composite endpoint
87 defined as the occurrence of at least one of the following complications: severe post-partum
88 hemorrhage defined by the use of a blood transfusion, intensive care unit (ICU) admission or
89 death. To assess the association of gestational age <26 weeks and SMMM, we used
90 multivariate logistic regression and a propensity score matching approach.

91 **Results:** Among 2525 women having preterm cesareans, 116 before 26 weeks and 2409
92 between 26 and 34 weeks, 407 (14.4%) presented SMMM. SMMM occurred in 31 (26.7%)
93 mothers who were at gestational age < 26 weeks vs 376 (14.2%) between 26 and 34 weeks
94 ($p < .001$). Multivariate logistic regression showed significant association of gestational age <
95 26 weeks and SMMM (adjusted odds ratio [aOR] 2.50, 95% Confidence Interval [95%CI]
96 1.42-4.40) and propensity score matching analysis was consistent with these results (aOR
97 2.27, 95% CI 1.31-3.93).

98 **Conclusion:** Obstetricians should know about the higher SMMM associated with cesareans
99 before 26 weeks, integrate it into the decision for cesarean delivery and be trained to manage
100 these complications.

101 **Keywords:** Cesarean, prematurity, extreme prematurity, severe maternal morbidity

102 **TEXT:**

103 **INTRODUCTION**

104 Management of preterm infants has greatly improved over the past years with more and more
105 active management provided for infants born at extreme gestational ages.¹⁻⁵ Active antenatal
106 care such as cesarean, in utero transfer and antenatal steroids initiated has been reported to be
107 associated with improved neonatal survival before 26 weeks of gestation (weeks).^{6,7} In this
108 context, cesarean rates at extreme prematurity have regularly increased these last few years.¹⁻⁴
109 However, cohort studies of preterm infants reported variable rates of cesarean and especially
110 between 23 and 25 weeks with noticeably lower rates for British (EPICURE 2)¹ and French
111 cohorts (EPIPAGE 2)^{5,8} compared to American (NIHCHD)² and Swedish cohorts
112 (EXPRESS).³ These heterogeneous care practices are observed across but also within
113 countries and can be related to reserved neonatal prognosis before 26 weeks and supposed
114 maternal risks of cesareans at these extreme gestational ages.

115 Regardless of gestational age, an increase in cesarean rate has been reported as being
116 associated with severe maternal morbidity (SMMM)⁹ but there is a paucity of data on SMMM
117 of extreme preterm cesareans, particularly before 26 weeks. Operative complications of these
118 cesareans have been reported with the use of a vertical incision in the upper uterine segment
119 often needed¹⁰⁻¹² and frequent difficulties of delivery because of fetal malpresentations and
120 the not yet formed lower uterine segments. Therefore, we hypothesize that the risk of SMMM
121 for cesarean is higher before 26 weeks than for older gestational ages but the comparison with
122 cesarean performed between 26 and 34 weeks has never been studied. Scientific societies also
123 recommended showing an interest in SMMM of these extreme preterm cesareans.¹³

124 The objective of this study was to investigate whether a gestational age of less than 26 weeks
125 is an independent risk factor for SMMM of preterm cesarean delivery, by performing a
126 secondary analysis of the national population-based cohort of preterm infants, EPIPAGE 2 .⁴

127 **MATERIALS AND METHODS**

128

129 **STUDY POPULATION AND SETTING**

130 The « Etude Epidémiologique sur les Petits Ages Gestationnels 2 » (EPIPAGE-2) is a
131 prospective national population-based cohort study of preterm infants born between 22 and 34
132 completed weeks of gestational age in France in 2011 (all French regions except one)
133 including pregnancy terminations, stillbirths and live births.⁴ Obstetrical and post-partum data
134 of mothers were also collected. Infants born at 22-26 weeks, 27-31 weeks and 32-34 weeks
135 were recruited for 8 months, 6 months and 5 weeks respectively.⁴ Details about the design and
136 methods have been published elsewhere.⁸ The committee for the protection of people
137 participating in biomedical research (CPP: March 18, 2011, ref SC-2873) approved this study.
138 For this analysis, we included all mothers of preterm infants born by cesarean between 22 and
139 34 weeks enrolled in the EPIPAGE 2 cohort, excluding mothers giving birth to twins having a
140 cesarean only for the second twin and pregnancy terminations.

141

142 **DATA COLLECTION**

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

152 coordination team used a centralized system to monitor and validate inclusions and data
153 collection at the national level.

154

155 **OUTCOME AND OTHER STUDIED FACTORS**

156 Severe maternal morbidity and Mortality (SMMM) was analyzed as a composite endpoint
157 defined as the occurrence of one of the following complications: severe post-partum
158 hemorrhage defined by the use of a blood transfusion, intensive care unit (ICU) admission or
159 death.

160 The main factor studied was gestational age of cesarean classified as < 26 weeks or ≥ 26
161 weeks. The threshold of 26 weeks was chosen because of clinical relevance given the frequent
162 occurrence of technical difficulties for cesareans before 26 weeks.¹¹ Gestational age was the
163 best estimate, based on the date of the last menstrual period and an early prenatal
164 ultrasonogram.

165 The other factors studied were: maternal age, type of pregnancy (singleton or multiple), parity
166 and scarred uterus, active smoking, pregestational diabetes, hospitalization for hypertension,
167 type of prematurity (spontaneous or induced), type of anesthesia, maternal indication for
168 cesarean and level of maternity units as defined in France since 1998 (level III facility before
169 33 weeks, level II facility between 33 and 36 weeks, level II A facility with neonatal unit and
170 level II B with neonatal intensive care unit, and level I without a neonatal department).

171

172 **STATISTICAL ANALYSIS**

173 We first described and compared maternal and maternity unit characteristics by gestational
174 age < 26 weeks or ≥ 26 weeks and then by SMMM. Categorical variables were compared with
175 the χ^2 test or Fisher exact test as appropriate. For continuous variables, data were analyzed
176 with t tests and Wilcoxon tests as appropriate. To account for the inclusion scheme of the

177 study and for representative preterm birth in France, a weighted coefficient was calculated
178 according to the length of the inclusion period and allocated to each individual (1 for births
179 between 22 and 26 weeks, 1.346 for births between 27 and 31 weeks and 7 for births between
180 32 and 34 weeks).

181 Then the main analysis consisted of a multivariate logistic regression model to quantify the
182 association between gestational age with the threshold of 26 weeks and SMMM with adjusted
183 ORs (aOR) and 95% confidence intervals (95% CI). The variables included in the
184 multivariate model were: gestational age with the threshold of 26 weeks, variables chosen
185 according to their clinical relevance and variables with a $p < 0.20$ in the univariate analysis.

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

190 As a secondary analysis, to control for potential indication bias, we used a propensity score
191 matching approach (method optimal, ratio 1:10) to check for baseline confounding factors
192 that might influence either SMMM or delivery before 26 weeks. The propensity score was
193 based on the following baseline factors: maternal age, type of pregnancy (singleton vs
194 multiple), parity and scarred uterus, active smoking, pregestational diabetes, hospitalization
195 for hypertension (only one variable used to evaluate hypertensive pathology to avoid over-
196 adjustment and to limit measurement bias), type of prematurity (spontaneous or induced) and
197 maternal indication for cesarean. The propensity score considered gestational age (< 26 weeks
198 versus ≥ 26 weeks) as a dependent variable and was defined as the probability that the
199 cesarean would have been performed at an extreme preterm gestational age depending on
200 woman's baseline characteristics.¹⁴ A model was then proposed on the matched sample with
201 SMMM as a dependent variable, gestational age (< 26 weeks versus ≥ 26 weeks) as the

202 primary exposure of interest and general anesthesia (post-baseline factor associated with the
203 act of cesarean) as an independent variable. There were no missing data for gestational age,
204 maternal age, type of pregnancy, scarred uterus and type of maternity unit. Missing data were
205 not specifically addressed because it corresponded to less than 5% of data.
206 Data were analyzed using R Studio V.1.0.44 and survey package for the specific design of the
207 study. Statistical significance was set at two-tailed $p < .05$.

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214 **RESULTS**215 *Description of the population, maternity units and cesarean rates*

216 Among the 4620 mothers included in EPIPAGE 2 study, 2548 (56.2%) had Cesareans
217 between March and December 2011.

218 Our study included 2525 mothers (Figure 1) after the exclusion of 23 mothers who had a
219 Cesarean only for the second twin: 116 (16.0%) between 22 and 25 weeks, 429 (63.6%)
220 between 26 and 27 weeks, 1456 (69.8%) between 28 and 31 weeks and 524 (54.2%) between
221 32 and 34 weeks.

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

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

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

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

230 Gestational age < 26 weeks was significantly associated with SMMM, general anesthesia and
231 type III of maternity units whereas women having cesarean between 26 and 34 weeks more
232 frequently presented pregestational diabetes, hospitalization for hypertension and induced
233 prematurity.

234 The main indications for cesareans before 26 weeks were: (i) systematic because of the
235 gestational age (obstetrical decision based only on prematurity), fetal presentation or multiple
236 pregnancy in 29 (27.9%), (ii) non reassuring fetal heart rate in 9 (8.6%), (iii) arrest of labor in
237 2 (1.9%), (iv) fetal pathology in 7 (6.7%), (v) maternal pathology in 27 (26.0%) and (vi)
238 others in 30 (28.8%) cases.

239 The main indications for cesareans between 26 and 34 weeks were: (i) systematic because of
240 gestational age, fetal presentation or multiple pregnancy in 315 cases (12.5%), (ii) non
241 reassuring fetal heart rate in 397 (18.5%), (iii) arrest of labor in 30 (1.8%), (iv) fetal pathology
242 in 385 (17.4%), (v) maternal pathology in 696 (26.0%) and (vi) others in 389 (32.5%) cases.
243 The most common maternal indications for preterm cesareans were: preeclampsia, eclampsia,
244 Hellp syndrome, diabetes and placenta praevia.
245 Fetal presentation was breech in 57 cases (53.3%) before 26 weeks and in 723 (27.8%)
246 between 26 and 34 weeks and other presentations such as transverse lie in 11 cases (10.3%)
247 before 26 weeks and 135 cases (5.7%) between 26 and 34 weeks ($p < .001$). Difficulties in
248 delivery occurred in 10 cases (10.9%) before 26 weeks versus 110 (4.7%) between 26 and 34
249 weeks ($p = .07$).

250

251

252 Univariate and multivariate cluster analysis

253 The following factors were associated with SMMM: gestational age before 26 weeks ($p <$
254 $.001$), hospitalization for hypertension ($p < .001$), induced prematurity ($p < .01$), general
255 anesthesia ($p < .001$) and maternal indication for cesarean ($p < .001$). No significant
256 association was found between type of uterine incision and SMMM ($p = .77$).

257 After the multivariate cluster analysis, the mothers having a cesarean before 26 weeks
258 presented more than a twofold increase in the risk of SMMM compared with those having a
259 cesarean between 26 and 34 weeks (Tables 2 and 3) (aOR 2.50 95% CI 1.42-4.44, $p = 0.001$).

260 The other variables statistically associated with SMMM were: pregestational diabetes (aOR
261 2.64, 95% CI 1.02-6.60), hospitalization for hypertension (aOR 2.66, 95% CI 1.83-3.85),
262 general anesthesia (aOR 3.41, 95% CI 2.37-4.91) and maternal indication for cesarean (aOR
263 2.22, 95% CI 1.44-3.43). The other variables included in the multivariate analysis were: type

264 of pregnancy (singleton vs multiple), parity and scarred uterus, active smoking, and
265 prematurity (spontaneous vs induced).

266 Considering gestational age according to 3 modalities showed consistent results ($p=0.007$); in
267 comparison with the reference group of gestational age between 32 and 34 weeks, gestational
268 age <26 weeks was significantly associated with SMMM (aOR 2.50, 95% CI 1.41-4.45,
269 $p=0.002$), but no significant association between gestational age between 26 and 31 weeks
270 and SMMM was found (aOR 1.03, 95% CI 0.68-1.56, $p=0.89$).

271

272 Propensity score matching approach

273 The results of this secondary analysis based on propensity score matching were consistent
274 with the previous results: gestational age <26 weeks was significantly associated with SMMM
275 in two different models: adjusted for a potential confounding factor related to cesarean
276 delivery (general anesthesia) (aOR 2.27, 95%CI 1.31-3.93) or not (aOR 3.11, 95% CI 1.84-
277 5.25).

278

279

280 **COMMENT**

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

284 The comparison of outcomes of cesareans before 26 weeks versus between 26 and 34 weeks
285 has never been evaluated in literature but appears more clinically relevant than a comparison
286 with term cesareans. The threshold of 26 weeks was chosen because of reported operative
287 complications of these cesareans with the frequent need for a vertical incision in the upper
288 uterine segment and frequent operative difficulties related to fetal malpresentations and the
289 not yet formed lower uterine segment for these periviable births.^{10,15-18} Classical incision on
290 the upper segment has been known to represent a higher risk of maternal complications
291 (infections, hemorrhage, blood transfusion and ICU admission).^{16,18-21}

292 To our knowledge, our study is the first to report this design analyzing SMMM of only
293 cesareans at extreme prematurity and to specifically investigate the association between
294 gestational age and maternal morbidity. In fact, a higher rate of maternal mortality related to
295 cesarean compared to vaginal delivery is established regardless of the age of pregnancy²²⁻²⁵
296 and association between prematurity and maternal morbidity has been reported regardless of
297 the mode of delivery and maybe related to an indication bias.^{11,24-26}

298 The strength of our study includes the specific prospective population-based cohort design,⁴
299 contrary to under-powered retrospective studies.²⁷ The number of mothers who had preterm
300 cesareans before 26 weeks ensured enough power to answer our initial hypothesis.

301 The external validity is high because EPIPAGE2 is a nationwide study and cluster analysis
302 took into account a potential center effect. It would be interesting to study SMMM in
303 American and Swedish cohorts with high proportions of cesarean before 26 weeks.

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

310 The originality of our study is the use of different statistical strategies to limit indication bias
311 that could affect maternal outcomes. The propensity score matching approach was used to
312 check for confounding factors that might influence either SMMM or delivery before 26
313 weeks. This strategy confirmed the association between SMMM and operative act of cesarean
314 and so regardless of prior maternal morbidity. Furthermore, gestational age < 26 weeks is an
315 independent factor of SMMM for cesareans whatever the type of maternal indication
316 (preeclampsia, eclampsia, hellp syndrome, diabetes, placenta praevia; data not provided
317 because of a large proportion of missing data). This leads us to believe that SMMM of
318 cesareans before 26 weeks is related to pre-operative maternal morbidity of these mothers but
319 also to operative difficulties of these cesareans. SMMM should be associated with the incision
320 on a preterm uterus whatever the type of incision. Furthermore, SMMM was associated with
321 gestational age < 26 weeks whether the prematurity was spontaneous or induced. Before
322 deciding on a cesarean, it therefore seems important to have shared decision-making and
323 weigh maternal morbidity, neonatal morbidity and survival at these vulnerable gestational
324 ages and particularly at periviable ages. Perlberg et al reported only 31% of infants were alive
325 at discharge at 24 weeks and 60% at 25 weeks during the same period.⁵ This information is
326 especially needed in case of spontaneous prematurity when spontaneous vaginal delivery is
327 feasible. A recent study reported a significant association between maternal complications and
328 spontaneous periviable birth regardless mode of delivery.²⁶ As recommended in the consensus

329 on obstetric care for periviable birth, decisions should include declining or accepting
330 interventions and therapies based on individual circumstances and individual values.²⁸

331 One of the limitations of our study was the evaluation of SMMM. The definition of SMMM is
332 not standardized in literature and is sometimes defined as blood transfusion and/or
333 hysterectomy to define severe post-partum hemorrhage, ICU admission, death and length of
334 hospitalization exceeding 7 days.²⁹ Other references defined SMMM as the occurrence of an
335 infection, surgical injury, endometritis, readmission^{11,30} or reopening or unexpected
336 procedure.¹¹ In our study, severe post-partum hemorrhage was defined by the need for blood
337 transfusion and not by estimated blood loss, initial hematocrit averages or hysterectomy
338 (which were not available in our data) and data were collected before a core outcome set was
339 developed and published.³¹ Furthermore, we did not choose maternal hospital stays exceeding
340 7 days because the length of stay could be related to neonatal hospitalization. Another
341 limitation was the evaluation of the severity of the pathology of women hospitalized for
342 hypertension before cesarean, because the variable “hospitalization for hypertension” was
343 chosen. Other variables (Hellp syndrome, eclampsia) were not chosen to evaluate
344 hypertensive pathology to avoid over-adjustment, to limit measurement bias and because
345 these variables presented more missing data than “hospitalization for hypertension”.

346 We reported SMMM in 14.4% of cases in our cohort, this is substantial and more specific
347 than prior studies describing 8.6% of serious complications regardless of the mode of
348 delivery.¹¹ Before 26 weeks, SMMM risk was more than twice as frequent as between 26 and
349 34 weeks, and because 20% of mothers had cesareans in type I and II maternity units, all
350 practitioners must be aware of the potential complications of preterm cesareans and be
351 prepared to manage them. Developing and implementing optimal management of these
352 patients along with training of practitioners are therefore needed because preterm cesareans
353 will never be performed exclusively in type III maternity units.

354 Only few studies, with low levels of evidence (because of small samples, retrospective
355 cohorts and case control studies), have investigated outcomes of subsequent pregnancies after
356 preterm cesarean delivery.³²⁻³⁴ The risks of uterine rupture, praevia placenta and/or accreta,
357 post-partum hemorrhage, hysterectomy, maternal death or in utero death were documented,
358 but gestational age of index cases of cesarean has not been confirmed to be an associated
359 factor. Other studies are therefore needed to answer this question.

360 As a conclusion, our study showed that gestational age < 26 weeks was an independent risk
361 factor of SMMM in cases of preterm cesareans. These results should encourage reflection on
362 obstetric management of these women by practitioners from all categories of maternity ward
363 and shared-decision making.

364 Other studies are required to evaluate mid- and long-term morbidity and outcomes of
365 subsequent pregnancies after these preterm cesareans.

366

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370 PhD (Inserm UMR 1153, Obstetrical, Perinatal and Pediatric Epidemiology Research Team (Epopé),
371 Center for Epidemiology and Statistics Sorbonne Paris Cité, DHU Risks in pregnancy, Paris Descartes
372 University, Unité de Recherche Clinique – Centre d’Investigations Cliniques P1419, Département
373 Hospitalo-Universitaire Risks in Pregnancy, Cochin Hotel-Dieu Hospital, Assistance Publique-
374 Hôpitaux de Paris, Paris F-75014, France), **Catherine Arnaud**, MD, PhD (Research Unit on Perinatal
375 Epidemiology, Childhood Disabilities and Adolescent Health, INSERM UMR 1027, Paul Sabatier
376 University, Toulouse, France), **Julie Blanc**, MD (Department of Obstetrics and Gynecology, Aix
377 Marseille University, Marseille, France), **Pascal Boileau**, MD, PhD (Department of Neonatal
378 Pediatrics, Poissy Saint Germain Hospital, France, EA7285 Versailles Saint Quentin en Yvelines
379 University, France), **Thierry Debillon**, MD, PhD (Department of Neonatal Pediatrics, University
380 Hospital, Grenoble, France), **Pierre Delorme**, MD, MSc (Inserm UMR 1153, Obstetrical, Perinatal
381 and Pediatric Epidemiology Research Team (Epopé), Center for Epidemiology and Statistics Sorbonne
382 Paris Cité, DHU Risks in pregnancy, Paris Descartes University, Department of Obstetrics and
383 Gynecology, Cochin, Broca, Hôtel Dieu Hospital, AP-HP, Paris, France), **Claude D’Ercole**, MD
384 (Department of Obstetrics and Gynecology, Nord Hospital, Assistance Publique des Hôpitaux de
385 Marseille (AP-HM), Aix Marseille Université, AMU, Marseille, France), **Thomas Desplanches**, RM,
386 MSc (Inserm UMR 1153, Obstetrical, Perinatal and Pediatric Epidemiology Research Team (Epopé),
387 Center for Epidemiology and Statistics Sorbonne Paris Cité, DHU Risks in pregnancy, Paris Descartes
388 University), **Caroline Diguisto**, MD, MSc (Inserm UMR 1153, Obstetrical, Perinatal and Pediatric
389 Epidemiology Research Team (Epopé), Center for Epidemiology and Statistics Sorbonne Paris Cité,
390 DHU Risks in pregnancy, Paris Descartes University, Maternité Olympe de Gouges, University
391 Francois Rabelais, Tours, France), **Laurence Foix-L’Hélias**, MD, PhD (Inserm UMR 1153,
392 Obstetrical, Perinatal and Pediatric Epidemiology Research Team (Epopé), Center for Epidemiology
393 and Statistics Sorbonne Paris Cité, DHU Risks in pregnancy, Paris Descartes University, Sorbonne
394 Universités, UPMC Univ Paris 06, IFD, 4 Place Jussieu, 75252 PARIS cedex 05, Paris, France,

395 Department of Neonatal Pediatrics, Trousseau Hospital, AP-HP, Paris, France), **Aurélie Garbi**, MD
396 (Department of Neonatology, Assistance Publique Hopitaux de Marseille, Marseille, France),
397 **Géraldine Gascoin**, MD, PhD (Department of Neonatal Medicine, Angers University Hospital,
398 Angers, France), **Adrien Gaudineau**, MD (Department of Obstetrics and Gynecology, Hautepierre
399 Hospital, Strasbourg, France), **Catherine Gire**, MD (Department of Neonatology, North Hospital,
400 Marseille, France), **François Goffinet**, MD, PhD (Inserm UMR 1153, Obstetrical, Perinatal and
401 Pediatric Epidemiology Research Team (Epopé), Center for Epidemiology and Statistics Sorbonne
402 Paris Cité, DHU Risks in pregnancy, Paris Descartes University, Department of Obstetrics and
403 Gynecology, Cochin, Broca, Hôtel Dieu Hospital, AP-HP, Paris, France), **Gilles Kayem**, MD, PhD
404 (Inserm UMR 1153, Obstetrical, Perinatal and Pediatric Epidemiology Research Team (Epopé),
405 Center for Epidemiology and Statistics Sorbonne Paris Cité, DHU Risks in pregnancy, Paris Descartes
406 University, Sorbonne Universités, UPMC Univ Paris 06, IFD, 4 Place Jussieu, 75252 PARIS cedex
407 05, Paris, France, Department of Obstetrics and Gynecology, Trousseau Hospital, AP-HP, Paris,
408 France), **Bruno Langer**, MD (Department of Obstetrics and Gynecology, Hautepierre Hospital,
409 Strasbourg, France), **Mathilde Letouzey**, MD, MSc (Department of Neonatal Pediatrics, Poissy Saint
410 Germain Hospital, France), **Elsa Lorthe**, RM, PhD (Inserm UMR 1153, Obstetrical, Perinatal and
411 Pediatric Epidemiology Research Team (Epopé), Center for Epidemiology and Statistics Sorbonne
412 Paris Cité, DHU Risks in pregnancy, Paris Descartes University), **Emeline Maisonneuve**, MD, MSc
413 (Department of Obstetrics and Gynecology, Trousseau Hospital, APHP, Paris, France), **Stéphane**
414 **Marret**, MD, PhD (Department of Neonatal Medicine, Rouen University Hospital and Région-
415 INSERM (ERI 28), Normandy University, Rouen, France), **Isabelle Monier**, RM, PhD (Inserm UMR
416 1153, Obstetrical, Perinatal and Pediatric Epidemiology Research Team (Epopé), Center for
417 Epidemiology and Statistics Sorbonne Paris Cité, DHU Risks in pregnancy, Paris Descartes
418 University), **Andrei Morgan**, MD, PhD (Inserm UMR 1153, Obstetrical, Perinatal and Pediatric
419 Epidemiology Research Team (Epopé), Center for Epidemiology and Statistics Sorbonne Paris Cité,
420 DHU Risks in pregnancy, Paris Descartes University), **Jean-Christophe Rozé**, MD, PhD (Department
421 of Neonatal Medicine, Nantes University Hospital, Nantes, France, Epidémiologie Clinique, Centre
422 d'Investigation Clinique (CIC004), Nantes University Hospital, Nantes, France), **Thomas Schmitz**,

423 MD, PhD (Inserm UMR 1153, Obstetrical, Perinatal and Pediatric Epidemiology Research Team
424 (Epopé), Center for Epidemiology and Statistics Sorbonne Paris Cité, DHU Risks in pregnancy, Paris
425 Descartes University, Department of Obstetrics and Gynecology, Robert Debré Hospital, Assistance
426 Publique-Hôpitaux de Paris, Paris, France), **Loïc Sentilhes**, MD, PhD (Department of Obstetrics and
427 Gynecology, Bordeaux University Hospital, Bordeaux, France), **Damien Subtil**, MD, PhD
428 (Department of Obstetrics and Gynecology, Jeanne de Flandre Hospital, Lille, France), **Héloïse**
429 **Torchin**, MD, MSc (Inserm UMR 1153, Obstetrical, Perinatal and Pediatric Epidemiology Research
430 Team (Epopé), Center for Epidemiology and Statistics Sorbonne Paris Cité, DHU Risks in pregnancy,
431 Paris Descartes University, Neonatal Medicine and Resuscitation Service in Port-Royal, Cochin
432 Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France), **Barthélémy Tosello**, MD
433 (Department of Neonatology, Assistance Publique Hopitaux de Marseille, Marseille, France),
434 **Christophe Vayssière**, MD, PhD (Department of Obstetrics and Gynecology, University Hospital,
435 Toulouse, France, Research Unit on Perinatal Epidemiology, Childhood Disabilities and Adolescent
436 Health, INSERM UMR 1027, Paul Sabatier University, Toulouse, France), **Norbert Winer**, MD, PhD
437 (Department of Obstetrics and Gynecology, University Hospital, INRA, UMR 1280 Physiologie des
438 adaptations nutritionnelles, Nantes, France), **Jennifer Zeitlin** (Inserm UMR 1153, Obstetrical,
439 Perinatal and Pediatric Epidemiology Research Team (Epopé), Center for Epidemiology and Statistics
440 Sorbonne Paris Cité, DHU Risks in pregnancy, Paris Descartes University).

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535 **Tables:**

536 Table 1. Maternal and unit characteristics by gestational age

Principal characteristics		< 26 weeks	≥ 26 weeks	p
		n= 116	n= 2409	
Maternal age (years), (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 of Cesarean, (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

537 SMMM, Severe Maternal Morbidity and Mortality

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

539 differential recruitment

540 Bold indicates significance (p<.05)

541

542

543 Table 2. Association of maternal and unit characteristics with severe maternal morbidity and
 544 mortality (SMMM)

Variables		Univariate analysis		
		« SMMM » group n = 407	« no SMMM » group n = 2118	p
Gestational age	≥ 26 weeks	376 (92.4)	2033 (96.0)	<.001
	< 26 weeks	31 (7.6)	85 (4.0)	
Maternal age (years)		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

Hospitalisation for hypertension		200 (49.1)	549 (25.9)	<.001
Placenta praevia		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		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 praevia		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)	

545 BMI, Body Mass Index ; SMMM, Severe Maternal Morbidity and Mortality

546 Data are n(%) or mean \pm standard deviations, all proportions are weighted according to differential recruitment

547 Bold indicates significance (p<.05)

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550 Table 3: Association between severe maternal morbidity and maternal characteristics

Variables	Cluster multivariate analysis	
	aOR ^a (95% CI)	
Maternal age (years)		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 of cesarean		2.22 (1.44-3.43)

551 ^a aOR, adjusted odds ratio for maternal age, type of pregnancy, parity and scarred uterus, gestational

552 age, active smocking, pregestational diabetes, hospitalization for hypertension, type of prematurity,

553 general anesthesia and maternal indication of cesarean ; CI, confidence interval

554 Bold indicates significance (p<.05)

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559 Figure 1: Flow chart of the study population

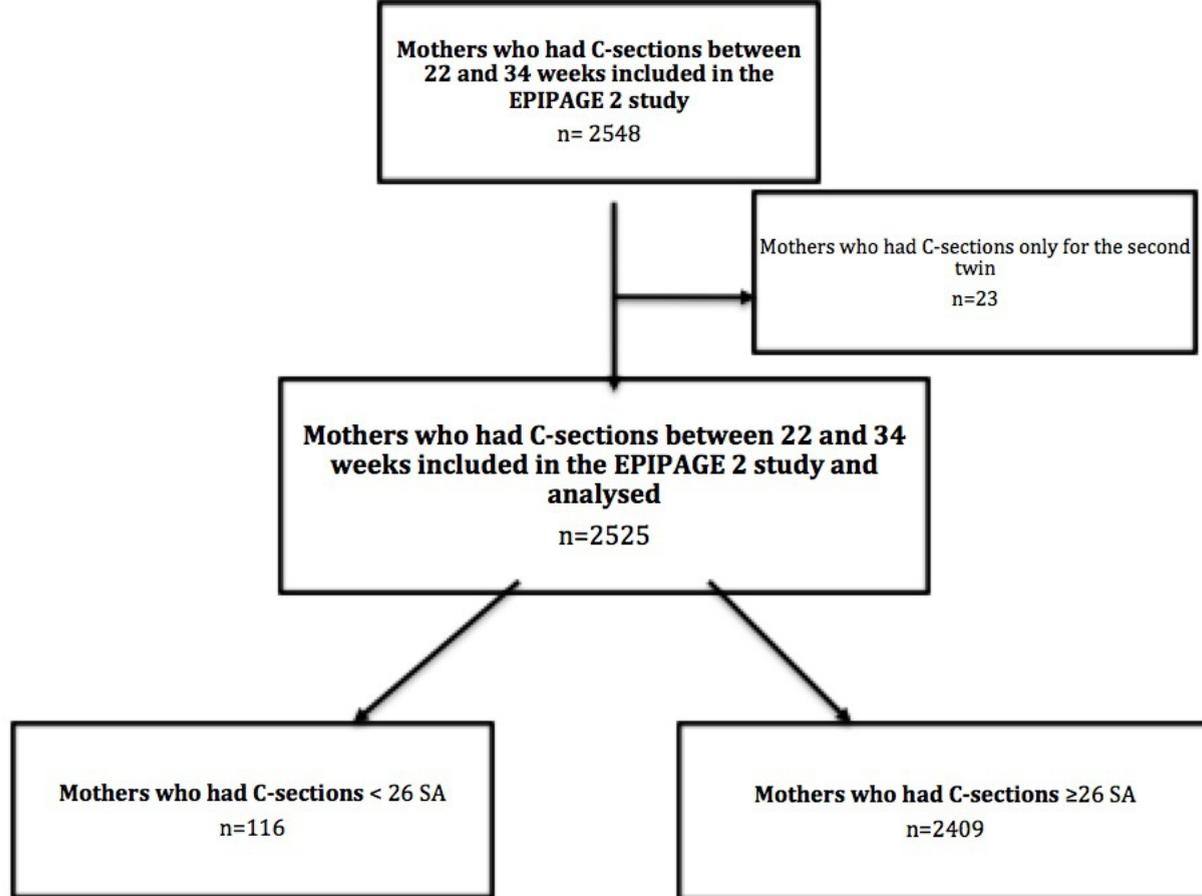


Figure 1: Flow chart of the study population