



# Severe maternal morbidity in preterm cesarean delivery: A systematic review and meta-analysis

Julie Blanc, Noémie Rességuier, Anderson Loundou, Laurent Boyer, Pascal Auquier, Barthélémy Tosello, Claude d'Ercole

## ► To cite this version:

Julie Blanc, Noémie Rességuier, Anderson Loundou, Laurent Boyer, Pascal Auquier, et al.. Severe maternal morbidity in preterm cesarean delivery: A systematic review and meta-analysis. European Journal of Obstetrics & Gynecology and Reproductive Biology, 2021, 261, pp.116–123. 10.1016/j.ejogrb.2021.04.022 . hal-03828877

**HAL Id: hal-03828877**

**<https://hal.science/hal-03828877>**

Submitted on 28 Feb 2023

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

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

1   **Title page**

2   **Severe maternal morbidity in preterm cesarean delivery: a systematic review and meta-**  
3   **analysis**

4   Julie Blanc<sup>1,2</sup>, Noémie Rességuier<sup>2</sup>, Anderson Loundou<sup>2</sup>, Laurent Boyer<sup>2</sup>, Pascal Auquier<sup>2</sup>,  
5   Barthélémy Tosello<sup>3,4</sup>, Claude d'Ercole<sup>1,2</sup>

6   <sup>1</sup> Department of Obstetrics and Gynecology, Nord Hospital, APHM, Chemin des Bourrely,  
7   13015 Marseille, France

8   <sup>2</sup> EA3279, CERESS, Health Service Research and Quality of Life Center, Aix-Marseille  
9   University, 13284 Marseille, France

10   <sup>3</sup> Department of Neonatology, North Hospital, Assistance Publique des Hôpitaux de  
11   Marseille, France

12   <sup>4</sup> Aix-Marseille Univ, CNRS, EFS, ADES, Marseille, France.

13   **Corresponding author:**

14   Julie Blanc, MD, PhD

15   Department of Obstetrics and Gynecology, Nord Hospital, APHM, chemin des Bourrely,  
16   13015 Marseille, France

17   EA 3279, Public Health, Chronic Diseases and Quality of Life, Research Unit, Aix-Marseille  
18   University, 13284 Marseille, France

19   +33 491964672, fax number +33 491964696

20   julie.blanc@ap-hm.fr ; ORCID: 0000-0002-1542-504X

21   **Declarations of interest: none**

22    **Highlights**

- 23        •    The incidence of extremely preterm cesarean delivery has increased
- 24        •    Gestational age under 26 weeks is associated with an increased risk of severe maternal
- 25           morbidity
- 26        •    Physicians should be aware of this risk to improve shared decision-making process.

# Severe maternal morbidity in preterm cesarean delivery: a systematic review and meta-analysis

Julie Blanc, Noémie Rességuier, Anderson Loundou, Laurent Boyer, Pascal Auquier, Barthélémy Tosello, Claude d'Ercole

## Abstract

*Objective:* More than half of extremely preterm infants are delivered by cesarean section. Few data are available about severe maternal morbidity (SMM) of these extremely preterm cesarean. The objective was to determine whether gestational age under 26 weeks of gestation (weeks) was associated with an increased risk of SMM compared with gestational age between 26 and 34 weeks in women having a cesarean delivery.

*Material and methods:* We searched MEDLINE, ISI Web of Science, the Cochrane Database, PROSPERO, and ClinicalTrials.gov on January 31, 2020. The search strategy clustered terms describing SMM and preterm cesarean delivery. No restrictions on language, publication status, and study design were applied. Abstracts were included if there was sufficient information to assess study quality. The authors of all identified studies were contacted to request for aggregated data. Relative risks (RR) were calculated using the inverse variance method. The primary outcome was SMM as defined in each study. We analyzed data on preterm cesarean deliveries between 22 and 34 weeks. The protocol was registered in PROSPERO (registration: CRD42019128644).

*Results:* Six studies involving 45,572 women (3,440 delivering < 26 weeks; 42,132 delivering between 26 and 34 weeks) were included. SMM occurred in 607 women (17.6%) < 26 weeks and 4,483 women (10.6%) between 26 and 34 weeks. Gestational age < 26 weeks was associated with an increased risk of SMM (RR, 1.65; 95% CI [Confidence Interval], 1.52–1.78;  $I^2 = 40\%$ ). Gestational age < 26 weeks remained associated with SMM in the subgroup

analyses depending on the type of the study (prospective or retrospective), country of the study (European or non-European), and high quality of the study. A sensitivity analysis showed that gestational age < 25 weeks was also associated with SMM in preterm cesarean delivery (RR, 1.66; 95% CI, 1.50–1.83;  $I^2 = 3\%$ ).

*Conclusions:* Gestational age < 26 weeks was associated with an increased risk of SMM in women having a preterm cesarean delivery. Obstetricians and neonatologists should be aware of the increased risk of SMM in cesarean.

**Keywords:** severe maternal morbidity, prematurity, extremely preterm birth, cesarean delivery

The protocol was registered in PROSPERO (registration: CRD42019128644).

## **Main Text**

### **1. Introduction**

The survival of very preterm infants born between 22 and 28 weeks of gestation (weeks) has increased worldwide in recent decades.<sup>1,2</sup> Among these infants, more than half are delivered by cesarean section.<sup>1-4</sup>

Periviable birth has been defined as delivery occurring between 20 0/7 weeks to 25 6/7 weeks.<sup>5</sup> A wide variation in practices regarding the active treatment has been reported and related to the between-hospital differences in survival and survival without impairment in these extreme gestational ages.<sup>6</sup> Cesarean delivery in case of fetal indications is one of such practices. Heterogeneous care practices could be related to the paucity of data on severe maternal morbidity (SMM) in periviable cesarean delivery, to poor neonatal survival and survival without impairment, and maybe to the preference of mothers and clinicians more considering the newborn in these clinical situations.<sup>7-11</sup>

The definition of SMM is not standardized in the literature and often referred to blood transfusion and/or hysterectomy in relation to severe postpartum hemorrhage, ICU admission, death, or unexpected procedures.<sup>7,8,11-13</sup> Some studies included infection criteria, any injury of adjacent organs, postnatal hypertensive complications, and/or thromboembolism events.<sup>7,9,12</sup>

The reported rate of SMM of preterm cesarean delivery were between 8 and 15%.<sup>7,13</sup> A recent analysis of World Health Organization surveys found that compared with vaginal delivery, cesarean delivery is associated with an increased risk of maternal intensive care unit (ICU) admission and maternal near miss in women with preterm singletons, without a significant difference in Apgar score < 7 at 5 minutes and neonatal death.<sup>14</sup> Operative complications of periviable cesarean deliveries have been reported and related to the use of an often-needed vertical incision in the upper uterine segment and fetal delivery difficulties.<sup>7,15,16</sup> We therefore hypothesize an increased risk of SMM in women having a cesarean delivery before 26 weeks

86 compared with women having a cesarean delivery between 26 and 34 weeks. We recently  
87 reported that mothers undergoing a cesarean delivery before 26 weeks experienced a more  
88 than twofold increase in the risk of SMM compared with those undergoing a cesarean  
89 delivery between 26 and 34 weeks.<sup>13</sup> We believe that other studies could help us obtain more  
90 evidence.<sup>7-11</sup> Furthermore, collecting more information about SMM in cesarean delivery at  
91 periviable ages is important for the shared decision-making process with parents facing the  
92 maternal and neonatal risks of extremely preterm birth.

93 The objective of this meta-analysis was to determine whether gestational age under 26 weeks  
94 was associated with an increased risk of SMM compared with a gestational age between 26  
95 and 34 weeks in women having a cesarean delivery.

## 2. Material and methods

### 2.1. Data sources

This systematic review and meta-analysis was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.<sup>17</sup>

The electronic databases MEDLINE, ISI Web of Science, the Cochrane Database, PROSPERO, and ClinicalTrials.gov were searched from the inception of each database until January 31, 2020. The following keywords were used: “Severe Maternal morbidity”, “Maternal morbidity”, “maternal mortality”, “extremely preterm”, “periviable”, “cesarean delivery”, “cesarean”, or “cesarean section”. The bibliographies of articles were checked.

### 2.2. Eligibility criteria and main outcome measures

Two investigators (JB and CDE) independently selected the articles and the purpose was to reproduce one individual’s results.

No restrictions on language, publication status, and study design were applied. Abstracts were included if there was sufficient information to assess study quality.

Studies that explored SMM in preterm cesarean delivery were eligible for inclusion. The exclusion criteria were studies dealing with neonatal outcomes only or long-term maternal morbidity only.

The primary outcome of this analysis was data on SMM (intraoperative adverse events and maternal short-term complications) as defined in each study and evaluated between 22 and 34 weeks.

### 2.3. Data collection and statistical analysis



All variables of interest concerning the studies and publications were independently extracted by two study authors (JB and NR) using a standardized form. The extracted data were authors, year of publication, sample size, type of study, period of inclusion, and country of the study.

The authors of all identified studies were contacted to request for data. We asked the authors for aggregated data, such as the numbers of women having preterm cesarean delivery and presenting SMM as well as the total numbers of women having preterm cesarean delivery per week of gestational age. These aggregated data were entered in the database by JB and the accuracy of the database was validated by NR. There was no patient involvement.

Two authors (JB and BT) assessed the risk of bias in each study. Study quality and risk of bias were evaluated for each study using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE),<sup>18</sup> and verified with the Tool to assess Risk of Bias in Cohort Study (Cochrane Database). In case of discrepancy, consensus was reached through a third investigator (NR). Identifying the risk of bias allows assessing the quality of a study based on the median, which is either high quality over the median (i.e., a low risk of bias,  $\geq 19$ ) or low quality under the median (i.e., a high risk of bias,  $< 19$ ).

Relative risks (RRs) with the fixed-effect model were calculated using the inverse variance method to evaluate the association of gestational age under 26 weeks and an increased risk of SMM.

Data analysis was performed using R (version 3.6.0) with meta package.

Heterogeneity between studies was quantified with the I-square statistic ( $I^2$ ), in which an  $I^2$  value lower than 0.50 was considered as a low risk of heterogeneity.<sup>19</sup> Publication bias was assessed by visual inspection of the funnel plot and use of the Egger test.<sup>20,21</sup>

A first sensitivity analysis was conducted using the leave-one-out method.

A second sensitivity analysis was performed to calculate the RRs and explore the association of gestational age under 25 weeks and SMM. This threshold of 25 weeks may be related to the evolution of clinical care, with active antenatal care practices increasing in recent years at earlier gestational ages.

Subgroup analyses were used to evaluate the following factors that moderated the association between gestational age and SMM: (1) type of cohort (retrospective or prospective), (2) country of the study (European or non-European), and (3) quality of the study (high vs. low quality according to the STROBE and Tool to assess Risk of Bias in Cohort Study).

The protocol was registered at PROSPERO registry (CRD42019128644) and can be accessed at [https://www.crd.york.ac.uk/prospERO/display\\_record.php?ID=CRD42019128644](https://www.crd.york.ac.uk/prospERO/display_record.php?ID=CRD42019128644). As a meta-analysis of existing data, our review was exempt from institutional review and there was no direct patient or public involvement.

### 3. Results

#### *3.1. General characteristics of the studies*

The electronic searches identified 369 articles, of which 277 were removed because they were duplicates and 80 were excluded after the abstract review. Twelve full texts were assessed for eligibility, of which nine were included after the agreement of the two independent investigators (Figure 1).

Because of the limited number of articles included, no article was excluded based on poor quality. After contacting the authors to request for data, we excluded three articles from the meta-analysis, as either the needed level of detail was not available in their datasets, or the authors no longer had access to their database. Six articles were finally eligible for the quantitative analysis (meta-analysis).

#### *3.2. Synthesis of the results*

The six included articles contained a broad variety of studied groups and evaluated outcomes described in Table 1. Four were retrospective cohort studies and two were prospective cohort studies involving a total of 45,572 women (3,440 delivering < 26 weeks; 42,132 delivering between 26 and 34 weeks). SMM occurred in 607 women (17.6%) < 26 weeks and 4,483 women (10.6%) between 26 and 34 weeks.

The details of the evaluation using the STROBE checklist and Tool to assess Risk of Bias in Cohort Study are presented in Table 1 and Figure 2.

No study addressed sample size calculation, and only two studies clearly addressed the potential source of bias and missing data.

Gestational age < 26 weeks was significantly associated with an increased risk of SMM (RR, 1.65; 95% CI, 1.52–1.78;  $I^2 = 40\%$ ) (Figure 3).

The funnel plot is reported in Figure 4, suggesting evidence of small-study effects, but this was not supported by the Egger's test ( $p = 0.46$ ).

The first sensitivity analysis conducted using the leave-one-out method confirmed the association between gestational age < 26 weeks and SMM by omitting each study one by one, and particularly by omitting the study with the biggest weight (Table 2).

This finding on gestational age < 26 weeks was confirmed with the analysis of gestational age < 25 weeks (RR, 1.66; 95% CI, 1.50–1.83;  $I^2 = 3\%$ ) (Figure 5).

Gestational age < 26 weeks remained associated with SMM in the subgroup analyses depending on the type of the study (prospective or retrospective), country of the study (European or non-European), and high quality of the study. The tests for heterogeneity between the two groups in terms of the type and country of the study were not significant. By contrast, the test for heterogeneity between the two groups in terms of quality of the study was significant, with high-quality articles presenting higher RR compared with the low-quality articles (Table 3).

## 4. Discussion

### 4.1. Main Findings

In this meta-analysis, we demonstrated that gestational age < 26 weeks was associated with an increased risk of SMM compared with a gestational age between 26 and 34 weeks. Furthermore, gestational age < 25 weeks was associated with SMM in preterm cesarean delivery. We showed that the association between gestational age < 26 weeks and SMM remained stable in the subgroup analyses.

### 4.2. Strengths and Limitations

To our knowledge, this is the first systematic review and meta-analysis of SMM in preterm cesarean delivery. We performed this study using a structured search strategy and predefined eligibility criteria. We followed PRISMA guidelines and included trials without restrictions on publication date or language. To confirm our hypothesis, we used sensitivity and subgroup analyses.

The limitations of this study are inherent in meta-analyses and the included studies. Three studies were evaluated to be of low quality based on the STROBE checklist and Tool to assess Risk of Bias in Cohort Study. The test for heterogeneity between the two groups of studies in terms of quality was significant, but we can presume that the pooled RR is reliable because the RR is very close to that of the group of high-quality studies. One study represented a weight of 77.8% but the first sensitivity analysis using the leave-one-out method allowed us to verify the strength of our main analysis.

One limitation is the variable definition of SMM in each study. The definition of SMM is not standardized in the literature, and we chose to respect the definitions used in each article but there are common criteria between articles as shown in Table S1. SMM often referred to

blood transfusion and/or hysterectomy in relation to severe postpartum hemorrhage, ICU admission, death, or unexpected procedures. Some studies included infection criteria, any injury of adjacent organs, postnatal hypertensive complications, and/or thromboembolism events. The study by Hesselman et al. used sepsis as inclusion criteria for SMM.<sup>9</sup> However, 3 of the 6 included studies included chorioamnionitis and/or endometritis as criteria for SMM.<sup>7,8,11</sup> Including infections as SMM is questionable since chorioamnionitis and endometritis are common complications of cesarean delivery and early preterm delivery may be necessitated by chorioamnionitis or may be the cause of preterm labor. Another limitation is that we could not use the recency of the inclusion period as a factor for the subgroup analysis; a relevant threshold could not be identified because of the large and old inclusion period of some studies, which was from 1998 for the oldest to 2015 for the most recent. Last, as pointed by Evans *et al*, the increased risk of maternal morbidity of extreme preterm cesarean could be attributable to pre-existing risk factors and some may be related with differences in operative details.<sup>22</sup> One limitation of the present study is so that it was not possible to adjust or control for comorbidities and confounding using aggregated data.

#### 4.3. Interpretation

The threshold of 26 weeks could be relevant for old and large included cohorts in Australia, France, Sweden, and the US between 1998 and 2015 but is probably not relevant nowadays. The management of preterm infants has greatly improved over the past years, with more and more active management being provided for infants born at extreme gestational ages and with improved neonatal survival without severe impairment before 26 weeks.<sup>1,2,4,23,24</sup> However, we demonstrated that gestational age under 25 weeks was associated with SMM in preterm cesarean delivery.

In some study, the authors excluded cesarean delivery due to maternal causes.<sup>7</sup> In other study, very few cesarean deliveries were performed in pregnancy with a periviable fetus.<sup>8</sup> So, the results of SMM may be conditioned by the cause of the cesarean. The design of this meta-analysis did not allow us to evaluate the effect of indication biases, but some included studies in this meta-analysis argued that SMM could be related to the surgical act of cesarean itself.<sup>7,8,10,11,13</sup> Preterm cesarean often includes a classical incision, which is—compared with a low transverse incision—known to be associated with an increased risk of SMM because of infection, postpartum hemorrhage, and ICU admission.<sup>7,25</sup> Furthermore, regardless of type, a deep myometrial incision is related to higher SMM.<sup>26</sup> The morphological changes in extracellular matrix materials in the uterine myometrium during pregnancy could also explain the morbidity of the surgical act of preterm cesarean, in which there is a high rate of collagen fibrils compared with elastic fibers.<sup>27</sup>

The subgroup analyses showed that the association between gestational age under 26 weeks and SMM remained significant depending on the country of the study (European or non-European), whereas a wide variation in practices regarding the active antenatal care, including cesarean delivery, has been reported at periviable ages.<sup>6</sup>

In 2007, the WHO has indicated that there is insufficient evidence to inform which mode of delivery is optimal for preterm infants.<sup>28</sup> Since then, the available data do not provide specific recommendations on the choice of delivery regardless of fetal presentation in case of spontaneous prematurity, which corresponds to 75% of preterm deliveries at periviable ages.<sup>3,29</sup> However, the literature allows using data for shared decision-making process with parents about survival rates at periviable ages.<sup>30</sup> This meta-analysis contributes to the body of knowledge on SMM in cesarean delivery. As stated by the Obstetric Care Consensus with regard to periviable birth, the “risks to a pregnant woman’s short-term and long-term health

need to be evaluated in the context of a newborn's predicted outcome and the degree to which the intervention in question is predicted to improve this outcome".<sup>31</sup>

In extremely preterm birth, women and couples need to face a *dual burden* according to Lyndon et al., which refers to neonatal morbidity in preterm birth in addition to SMM.<sup>32</sup> This dual burden occurs more often in cases of spontaneous preterm labor than in induced prematurity. Perinatal care should be coordinated with infant and maternal health care teams. Professionals should be aware of the maternal perceptions of the quality of health care in case of SMM and should find preventive measures for women, parents, and children facing extreme prematurity.<sup>33</sup>



## 5. Conclusions

This meta-analysis confirmed the association between gestational age < 26 weeks and SMM. The results should encourage reflection, research, and teamwork between neonatologists and obstetricians to improve the agreement between clinicians and the shared decision-making process with parents.

**Conflict of Interests statement:** the authors did not report any potential conflict of interest.

**Availability of Data and Materials:** Individual participant data will not be available because aggregated data were used in this meta-analysis

**Funding information:** None

**Author Contributions:** J.B., N.R., L.B., P.A., C.D.E. were responsible for the conception and design of this study. J.B., N.R., B.T. and C.D.E. were responsible for the data collection and data management. J.B., N.R., A.L. were responsible for conducting the analyses. All authors were involved in the interpretation of the data. J.B. drafted the initial manuscript, which was reviewed and critically revised by all authors. All authors approved the final manuscript as submitted. All authors gave agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Acknowledgements:** The authors acknowledge the authors of each study included in meta-analysis who accepted to provide data: Uma Reddy, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network, United States of America; Penelope Thomas and Scott Petersen, Mater Mother's Hospital, Raymond Terrace, South Brisbane, Queensland, Australia; Susanne Hesselman, Department of Women's and Children's Health, Uppsala University, SE-751 85 Uppsala, Sweden; Charline Bertholdt and Camille Le Ray, Obstetric and Gynecology Unit, Regional university Hospital Center of Nancy, Nancy, France and Port Royal Maternity Unit, Cochin Hospital, Paris-Descartes University, APHP, Paris, France; Robert Rossi, Center for Prevention of Preterm birth, perinatal institute, Cincinnati Children's Hospital Medical Center, and the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Cincinnati College of Medicine, Cincinnati, Ohio, United States of America. The authors acknowledge Scribendi to help editing English.

## References

1. Stoll, B. J. *et al.* Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics* **126**, 443–456 (2010).
2. Costeloe, K. L. *et al.* Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). *BMJ* **345**, e7976 (2012).
3. Ancel, P.-Y. *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.* **169**, 230–238 (2015).
4. EXPRESS Group *et al.* One-year survival of extremely preterm infants after active perinatal care in Sweden. *JAMA* **301**, 2225–2233 (2009).
5. Raju, T. N. K., Mercer, B. M., Burchfield, D. J. & Joseph, G. F. 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.* **123**, 1083–1096 (2014).
6. Rysavy, M. A. *et al.* Between-hospital variation in treatment and outcomes in extremely preterm infants. *N. Engl. J. Med.* **372**, 1801–1811 (2015).
7. Reddy, U. M. *et al.* Serious maternal complications after early preterm delivery (24–33 weeks' gestation). *Am. J. Obstet. Gynecol.* **213**, 538.e1–9 (2015).
8. Thomas, P. E., Petersen, S. G. & 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.* **56**, 60–68 (2016).
9. Hesselman, S., Jonsson, M., Råssjö, E.-B., Windling, M. & Högberg, U. Maternal complications in settings where two-thirds of extremely preterm births are delivered by cesarean section. *J. Perinat. Med.* **45**, 121–127 (2017).
10. Bertholdt, C. *et al.* Intraoperative adverse events associated with extremely preterm cesarean deliveries. *Acta Obstet. Gynecol. Scand.* **97**, 608–614 (2018).
11. Rossi, R. M. & DeFranco, E. A. Maternal Complications Associated With Periviable Birth. *Obstet. Gynecol.* **132**, 107–114 (2018).
12. Kawakita, T. *et al.* Maternal outcomes associated with early preterm cesarean delivery. *Am. J. Obstet. Gynecol.* **216**, 312.e1–312.e9 (2017).
13. Blanc, J. *et al.* Association between gestational age and severe maternal morbidity and mortality of preterm cesarean delivery: a population-based cohort study. *Am. J. Obstet. Gynecol.* (2019) doi:10.1016/j.ajog.2019.01.005.
14. Thanh, B. Y. L. *et al.* Mode of delivery and pregnancy outcomes in preterm birth: a secondary analysis of the WHO Global and Multi-country Surveys. *Sci. Rep.* **9**, 15556 (2019).
15. Bethune, M. & Permezel, M. The relationship between gestational age and the incidence of classical caesarean section. *Aust. N. Z. J. Obstet. Gynaecol.* **37**, 153–155 (1997).
16. Baeza, C. *et al.* [Obstetrical prognosis of patients after a previous caesarean section performed before 32 weeks of amenorrhea]. *Gynecol. Obstet. Fertil.* **44**, 629–635 (2016).
17. Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* **339**, b2535 (2009).
18. Adams, A. D., Benner, R. S., Riggs, T. W. & Chescheir, N. C. Use of the STROBE Checklist to Evaluate the Reporting Quality of Observational Research in Obstetrics. *Obstet. Gynecol.* **132**, 507–512 (2018).
19. Higgins, J. P. T. Measuring inconsistency in meta-analyses. *BMJ* **327**, 557–560 (2003).
20. Egger, M., Davey Smith, G., Schneider, M. & Minder, C. Bias in meta-analysis

- detected by a simple, graphical test. *BMJ* **315**, 629–634 (1997).
21. Guyatt, G. H. *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* **336**, 924–926 (2008).
  22. Evans, L. C. & Combs, C. A. Increased maternal morbidity after cesarean delivery before 28 weeks of gestation. *Int. J. Gynaecol. Obstet. Off. Organ Int. Fed. Gynaecol. Obstet.* **40**, 227–233 (1993).
  23. Ancel, P.-Y., Goffinet, F., & EPIPAGE 2 Writing Group. EPIPAGE 2: a preterm birth cohort in France in 2011. *BMC Pediatr.* **14**, 97 (2014).
  24. Perlberg, J. *et al.* Delivery room management of extremely preterm infants: the EPIPAGE-2 study. *Arch. Dis. Child. Fetal Neonatal Ed.* **101**, F384-390 (2016).
  25. Luthra, G., Gawade, P., Starikov, R. & Markenson, G. Uterine incision-to-delivery interval and perinatal outcomes in transverse versus vertical incisions in preterm cesarean deliveries. *J. Matern.-Fetal Neonatal Med. Off. J. Eur. Assoc. Perinat. Med. Fed. Asia Ocean. Perinat. Soc. Int. Soc. Perinat. Obstet.* **26**, 1788–1791 (2013).
  26. Sirgant, D. *et al.* Lower gestational age is associated with severe maternal morbidity of preterm cesarean delivery. *J. Gynecol. Obstet. Hum. Reprod.* 101764 (2020) doi:10.1016/j.jogoh.2020.101764.
  27. Nishinaka, K. & Fukuda, Y. Changes in extracellular matrix materials in the uterine myometrium of rats during pregnancy and postparturition. *Acta Pathol. Jpn.* **41**, 122–132 (1991).
  28. Villar, J. *et al.* Maternal and neonatal individual risks and benefits associated with caesarean delivery: multicentre prospective study. *BMJ* **335**, 1025 (2007).
  29. Mottet, N. & Riethmuller, D. [Mode of delivery in spontaneous preterm birth]. *J. Gynecol. Obstet. Biol. Reprod. (Paris)* **45**, 1434–1445 (2016).
  30. Younge, N. *et al.* Survival and Neurodevelopmental Outcomes among Periviable Infants. *N. Engl. J. Med.* **376**, 617–628 (2017).
  31. American College of Obstetricians and Gynecologists & Society for Maternal-Fetal Medicine. Obstetric Care consensus No. 6: Periviable Birth. *Obstet. Gynecol.* **130**, e187–e199 (2017).
  32. Lyndon, A. *et al.* A population-based study to identify the prevalence and correlates of the dual burden of severe maternal morbidity and preterm birth in California. *J. Matern.-Fetal Neonatal Med. Off. J. Eur. Assoc. Perinat. Med. Fed. Asia Ocean. Perinat. Soc. Int. Soc. Perinat. Obstet.* 1–9 (2019) doi:10.1080/14767058.2019.1628941.
  33. Norhayati, M. N., Surianti, S. & Nik Hazlina, N. H. Metasynthesis: Experiences of Women with Severe Maternal Morbidity and Their Perception of the Quality of Health Care. *PloS One* **10**, e0130452 (2015).

400    **Legends of Tables/Figures**

401    Table 1: Characteristics of studies included in quantitative analysis

402    Table 2. Sensitivity analysis using the leave-one-out method.

403    Table 3. Subgroup analyses of Risk of severe maternal morbidity of cesarean < 26 weeks vs ≥  
404    26 weeks

405    Figure 1: Flow diagram of studies through review process

406    Figure 2. Quality assessment of included studies according to STROBE checklist

407    Figure 3. Forest plot of RR for severe maternal morbidity of cesarean delivery < 26 weeks  
408    versus ≥ 26 weeks

409    Figure 4. The funnel plot of meta-analysis comparing the risk of severe maternal morbidity of  
410    cesarean delivery between < 26 weeks and ≥ 26 weeks

411    Figure 5. Forest plot of RR for severe maternal morbidity of cesarean delivery < 25 weeks  
412    versus ≥ 25 weeks

413 Table 1: Characteristics of studies included in quantitative analysis

Article	Sample size of the study	Sample size considered for meta-analysis	Type of study, number of centers, and period of inclusion	Country of the study	Characteristics of enrolled women	Gestational ages	Evaluated outcome	Quality category (STROBE check list and Tool to assess Risk of bias in cohort study)
Reddy et al, <sup>7</sup> 2015	1205	1198	Secondary analysis of observational prospective cohort, 25 medical centers, 2008 to 2011	United States	Women who had a live fetus on admission and delivered during the 24-hour period	23 to 33 weeks	Serious maternal complications: hemorrhage (blood loss $\geq 1500$ mL, blood transfusion or hysterectomy for hemorrhage), infection (endometritis, wound dehiscence or wound infection requiring antibiotics, re-opening or unexpected procedure), ICU admission or death	Low
Thomas et al, <sup>8</sup> 2016	265	265	Retrospective cohort study in a single center, from January 1998 to December 2009	Australia	Mothers of all liveborn neonates with a prenatally determined plan for active resuscitation	23 to 26 weeks	Composite maternal adverse outcome: death, adult ICU admission, sepsis, hysterectomy, transfusion, postpartum hemorrhage $> 1000$ mL, surgical injury, unplanned procedures/return to	Low

							theatre, endometritis, or postnatal hypertensive complication requiring treatment and readmission to hospital	
Hesselman et al, <sup>9</sup> 2017	406	395	Retrospective cohort study, 2 centers, 2001 to 2012	Sweden	Single and multiple extremely preterm deliveries at 22-27 weeks	22 to 27 weeks	Composite of major maternal complications: blood loss $\geq 2000\text{mL}$ , sepsis, deep hematoma, re-operation, or thromboembolism	Low
Bertholdt et al, <sup>10</sup> 2018	288	288	Retrospective cohort study, 1 hospital, January 2007 to March 2015	France	All extremely early cesarean deliveries during the period	24 to 27 weeks	Composite intraoperative adverse event: classical uterine incision, transplacental incision, difficulty in fetal extraction, postpartum hemorrhage (loss $\geq 500\text{mL}$ ), need for transfusion or any injury of adjacent organs (gastrointestinal, urological or vascular)	High
Rossi et al, <sup>11</sup> 2018	78466	40901 (between 22 and 34 weeks)	Population-based retrospective cohort study, 2006 to 2015	United States	All live births in Ohio between 2006 and 2015 excluding cases with missing mode of delivery or gestational age at delivery	20 to term (only 22 to 34 weeks in the meta-analysis)	Composite adverse maternal outcome: choriomanionitis, blood product transfusion, unplanned hysterectomy, unplanned operative procedure, uterine rupture or maternal	High

							admission to an ICU	
Blanc et al, <sup>13</sup> 2019	2525	2525	National prospective population-based cohort study, 278 maternity units, 2011	France	Mothers of preterm infants born by cesarean delivery excluding mothers giving birth to twins having a cesarean delivery only for the second twin and women with pregnancy terminations	22 to 34 weeks	Composite outcome: severe postpartum hemorrhage (defined by the use of a blood transfusion), ICU admission or death	High

414 ICU Intensive Care Unit; SMM Severe Maternal Morbidity; STROBE Strengthening the Reporting of Observational Studies in Epidemiology



415 Table 2. Sensitivity analysis using the leave-one-out method.

<b>Studies</b>	<b>RR</b>	<b>95%-CI</b>	<b>p-value</b>	<b>Tau<sup>2</sup></b>	<b>I<sup>2</sup></b>	<b>Weight</b>
Omitting Reddy 2015	1.65	[1.53-1.79]	<0.0001	0.0196	49.3%	4.3%
Omitting Thomas 2016	1.66	[1.54-1.80]	<0.0001	0.0074	29.0%	2.2%
Omitting Hesselman 2017	1.66	[1.53-1.79]	<0.0001	0.0079	31.5%	1.1%
Omitting Bertholdt 2018	1.61	[1.49-1.75]	<0.0001	0.0084	24.7%	8.6%
Omitting Rossi 2019	1.65	[1.40-1.94]	<0.0001	0.0421	52.0%	77.8%
Omitting Blanc 2019	1.64	[1.52-1.78]	<0.0001	0.0235	51.6%	6.1%
Pooled estimate	1.65	[1.52-1.78]	<0.0001	0.0137	40.0%	100%

416

417 Table 3. Subgroup analyses of Risk of Severe Maternal Morbidity of cesarean < 26 weeks vs  
 418  $\geq 26$  weeks

Groups	RR	95% CI	p-value	heterogeneity
			between subgroups	
<b>Type of study</b>			0.81	
<b>Prospective (2 studies)</b>	1.60	1.26-2.04		
<b>Retrospective (4 studies)</b>	1.65	1.52-1.79		
<b>Country of the study</b>			0.29	
<b>Non-European (3 studies)</b>	1.62	1.49-1.76		
<b>European (3 studies)</b>	1.81	1.49-2.20		
<b>Quality of the study</b>			0.04	
<b>High quality (3 studies)</b>	1.68	1.55-1.83		
<b>Low quality (3 studies)</b>	1.24	0.94-1.65		

419 *RR, Relative Risk; CI, Confidence Interval*

Figure 1: Flow diagram of studies through review process

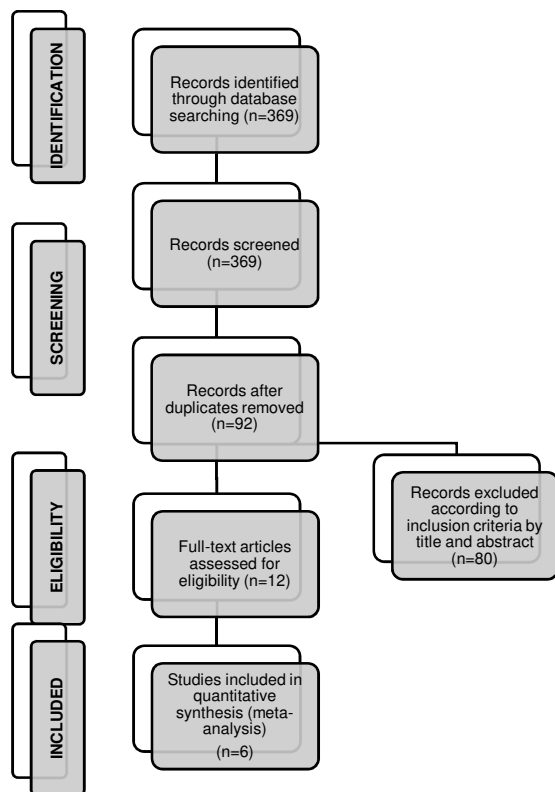
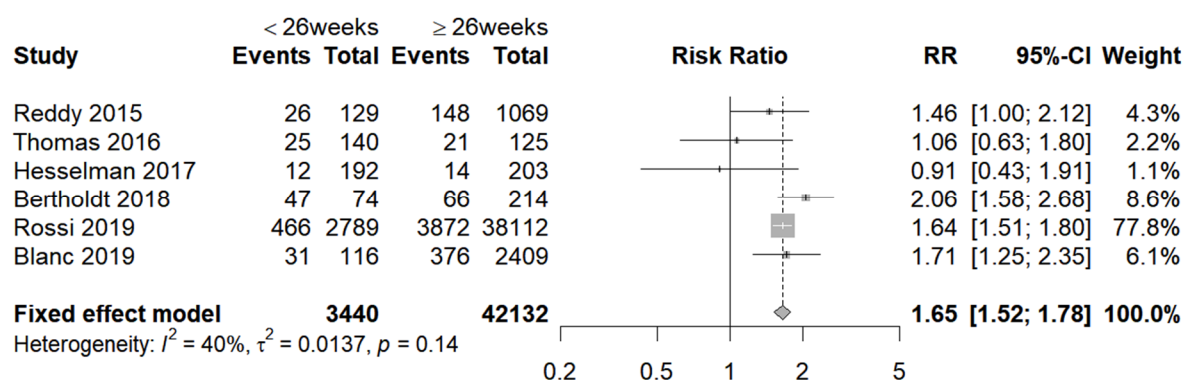


Figure 2. Quality assessment of included studies according to STROBE checklist



Figure 3. Forest plot of RR for severe maternal morbidity of cesarean delivery < 26 weeks versus ≥ 26 weeks



RR, Relative Risk ; CI, confidence interval

Figure 4. The funnel plot of meta-analysis comparing the risk of severe maternal morbidity of cesarean delivery between  $< 26$  weeks and  $\geq 26$  weeks

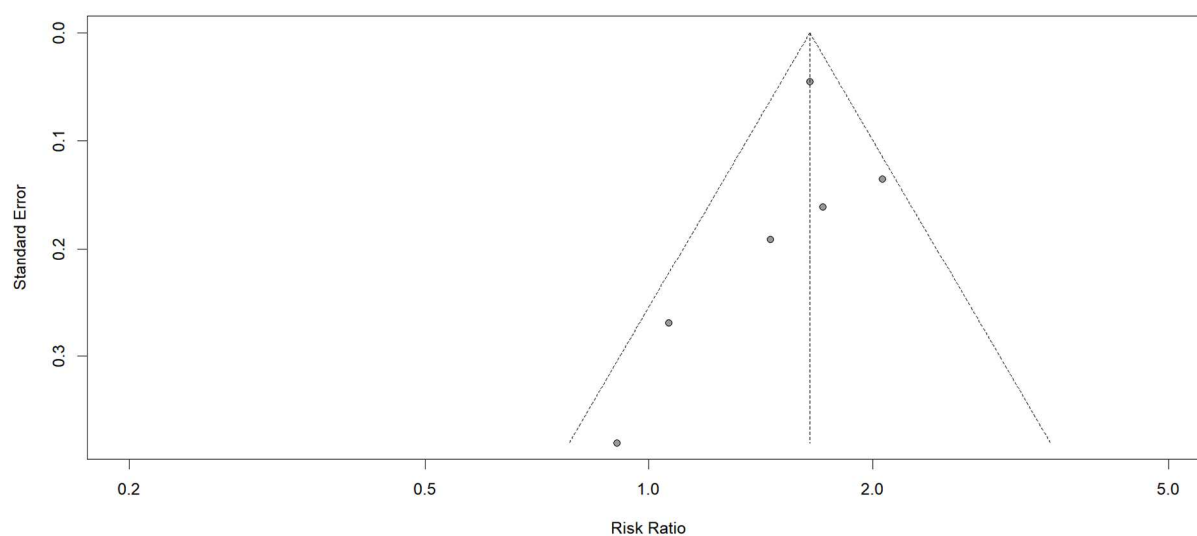
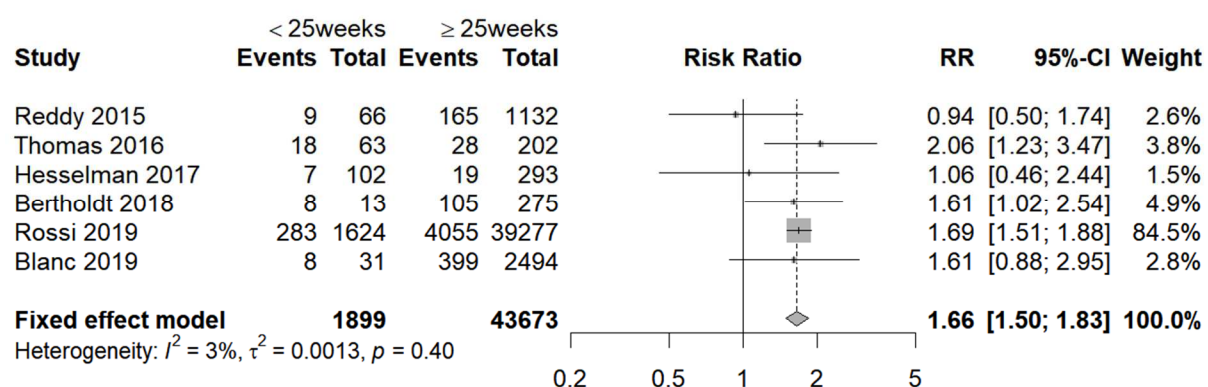


Figure 5. Forest plot of RR for severe maternal morbidity of cesarean delivery < 25 weeks versus ≥ 25 weeks



RR, Relative Risks ; CI, Confidence Interval