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1 **Title page**

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

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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.

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

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30 Barthélémy Tosello, Claude d'Ercole

31 **Abstract**

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

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

46 *Results:* Six studies involving 45,572 women (3,440 delivering < 26 weeks; 42,132 delivering
47 between 26 and 34 weeks) were included. SMM occurred in 607 women (17.6%) < 26 weeks
48 and 4,483 women (10.6%) between 26 and 34 weeks. Gestational age < 26 weeks was
49 associated with an increased risk of SMM (RR, 1.65; 95% CI [Confidence Interval], 1.52–
50 1.78; $I^2 = 40\%$). Gestational age < 26 weeks remained associated with SMM in the subgroup

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

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

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

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

61 **Main Text**

62 **1. Introduction**

63 The survival of very preterm infants born between 22 and 28 weeks of gestation (weeks) has
64 increased worldwide in recent decades.^{1,2} Among these infants, more than half are delivered
65 by cesarean section.¹⁻⁴

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

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

78 The reported rate of SMM of preterm cesarean delivery were between 8 and 15%.^{7,13} A recent
79 analysis of World Health Organization surveys found that compared with vaginal delivery,
80 cesarean delivery is associated with an increased risk of maternal intensive care unit (ICU)
81 admission and maternal near miss in women with preterm singletons, without a significant
82 difference in Apgar score < 7 at 5 minutes and neonatal death.¹⁴ Operative complications of
83 periviable cesarean deliveries have been reported and related to the use of an often-needed
84 vertical incision in the upper uterine segment and fetal delivery difficulties.^{7,15,16} We therefore
85 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.¹³ We believe that other studies could help us obtain more
90 evidence.⁷⁻¹¹ 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.

96 **2. Material and methods**

97

98 *2.1. Data sources*

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

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

106

107 *2.2. Eligibility criteria and main outcome measures*

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

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

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

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

118

119 *2.3. Data collection and statistical analysis*

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

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

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

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

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

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

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

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

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

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

156 **3. Results**

157

158 *3.1. General characteristics of the studies*

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

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

168

169 *3.2. Synthesis of the results*

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

175

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

178

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

181 Gestational age < 26 weeks was significantly associated with an increased risk of SMM (RR,
182 1.65; 95% CI, 1.52–1.78; $I^2 = 40\%$) (Figure 3).

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

185

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

189 This finding on gestational age < 26 weeks was confirmed with the analysis of gestational age
190 < 25 weeks (RR, 1.66; 95% CI, 1.50–1.83; $I^2 = 3\%$) (Figure 5).

191

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

199 **4. Discussion**

200

201 *4.1. Main Findings*

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

207

208 *4.2. Strengths and Limitations*

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

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

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

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

239

240 4.3. Interpretation

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

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

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

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

272 need to be evaluated in the context of a newborn’s predicted outcome and the degree to which
273 the intervention in question is predicted to improve this outcome”.³¹

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

281

282 **5. Conclusions**

283

284 This meta-analysis confirmed the association between gestational age < 26 weeks and SMM.

285 The results should encourage reflection, research, and teamwork between neonatologists and

286 obstetricians to improve the agreement between clinicians and the shared decision-making

287 process with parents.

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

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

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294 and data management. J.B., N.R., A.L. were responsible for conducting the analyses. All
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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, ⁷ 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 ≥ 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, ⁸ 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, ⁹ 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 2000mL, sepsis, deep hematoma, re-operation, or thromboembolism	Low
Bertholdt et al, ¹⁰ 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 500mL), need for transfusion or any injury of adjacent organs (gastrointestinal, urological or vascular)	High
Rossi et al, ¹¹ 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, ¹³ 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.

Studies	RR	95%-CI	p-value	Tau²	I²	Weight
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	
Type of study			0.81	
Prospective (2 studies)	1.60	1.26-2.04		
Retrospective (4 studies)	1.65	1.52-1.79		
Country of the study			0.29	
Non-European (3 studies)	1.62	1.49-1.76		
European (3 studies)	1.81	1.49-2.20		
Quality of the study			0.04	
High quality (3 studies)	1.68	1.55-1.83		
Low quality (3 studies)	1.24	0.94-1.65		

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

Figure 1: Flow diagram of studies through review process

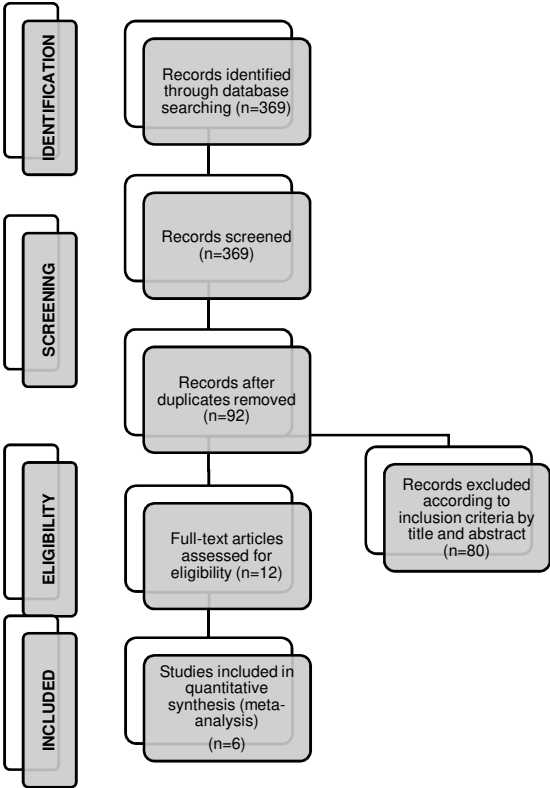


Figure 2. Quality assessment of included studies according to STROBE checklist

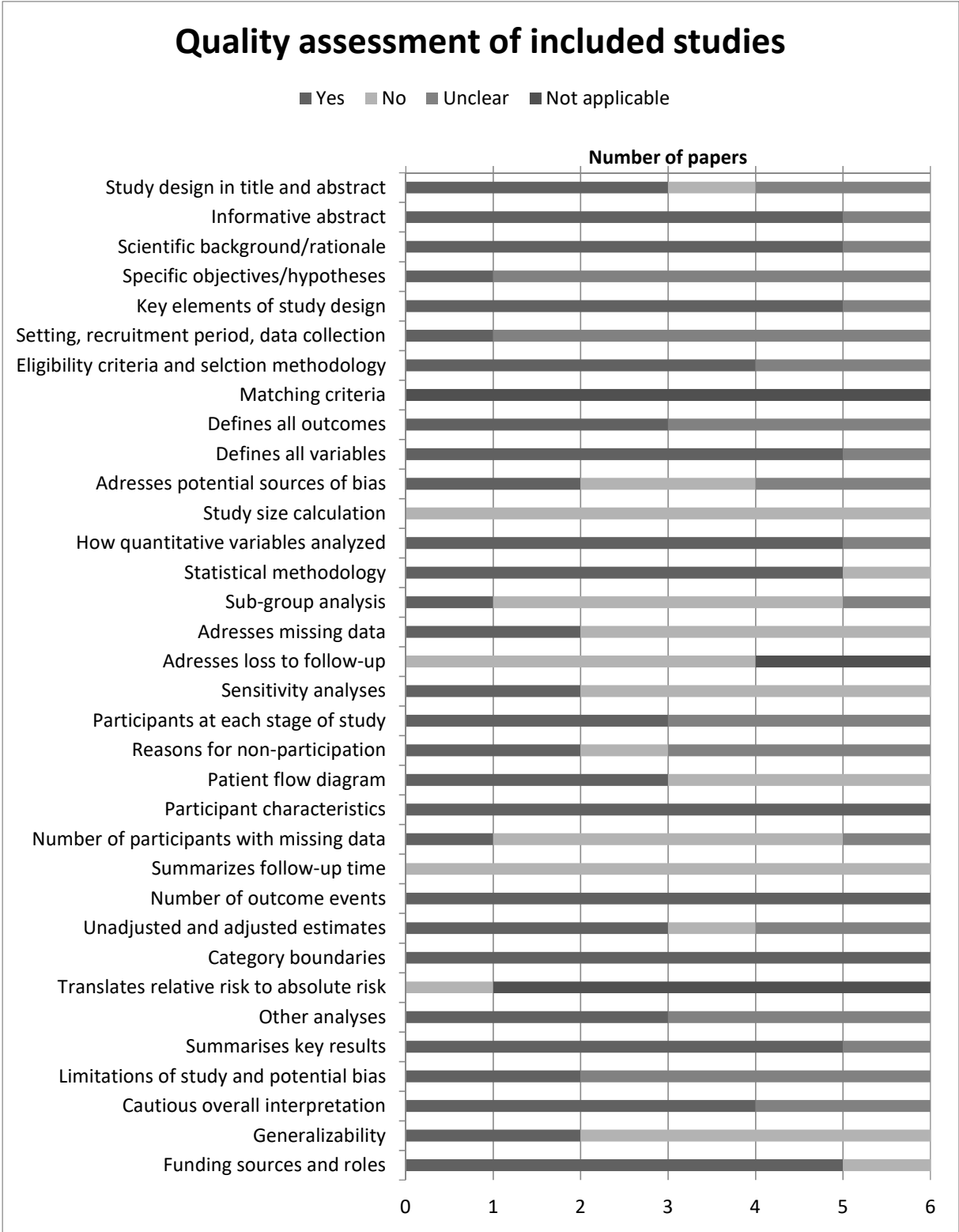
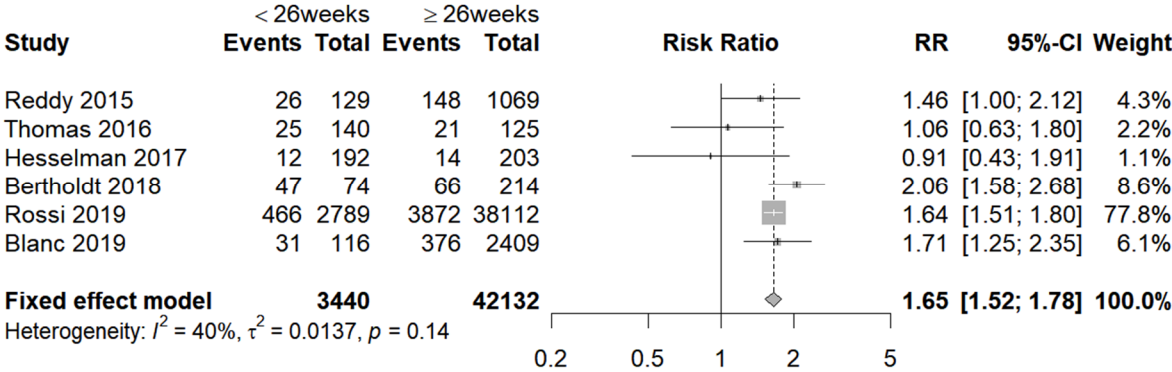


Figure 3. Forest plot of RR for severe maternal morbidity of cesarean delivery < 26 weeks versus ≥ 26 weeks



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

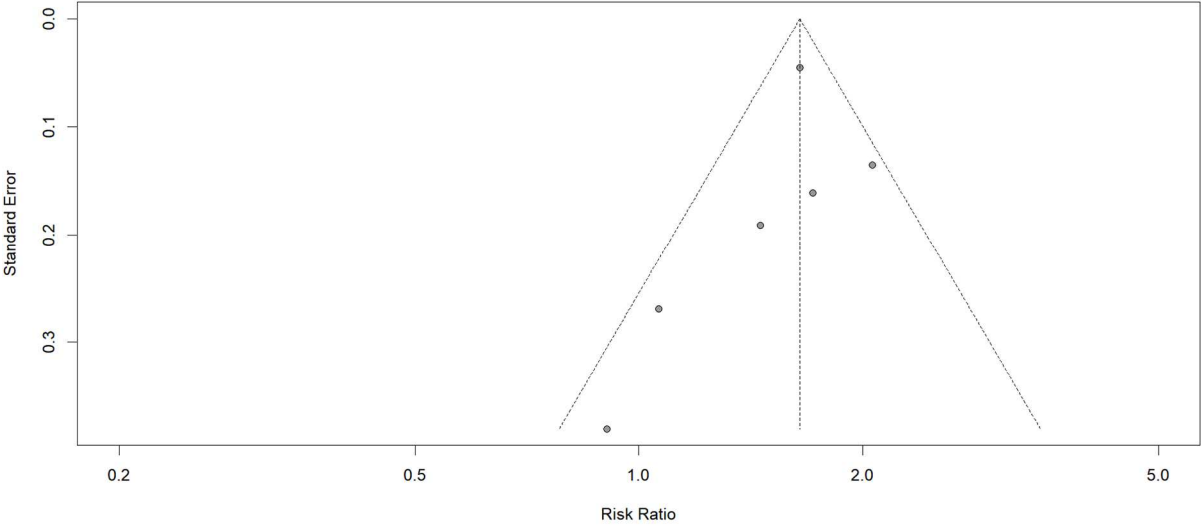
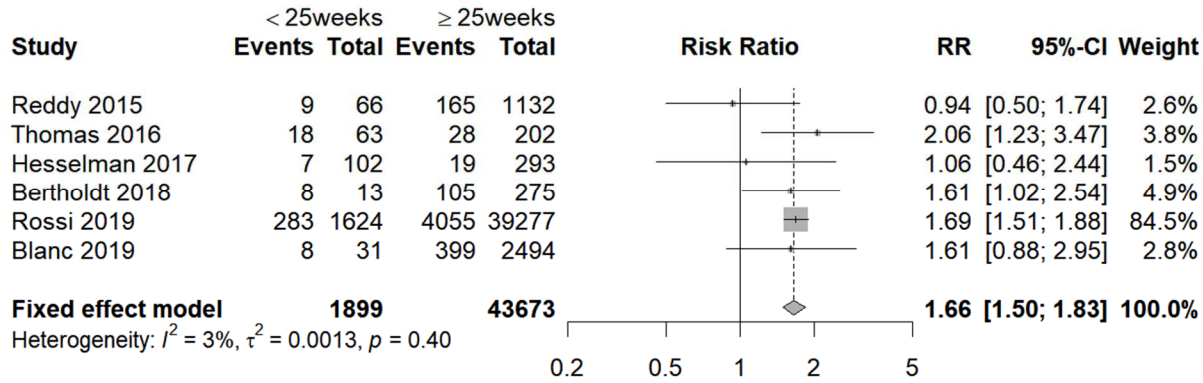


Figure 5. Forest plot of RR for severe maternal morbidity of cesarean delivery < 25 weeks versus ≥ 25 weeks



RR, Relative Risks ; CI, Confidence Interval