



Severe Acute Maternal Morbidity in Twin Compared With Singleton Pregnancies

Hugo Madar, François Goffinet, Aurélien Seco, Patrick Rozenberg, Corinne Dupont, Catherine Deneux-Tharaux

► To cite this version:

Hugo Madar, François Goffinet, Aurélien Seco, Patrick Rozenberg, Corinne Dupont, et al.. Severe Acute Maternal Morbidity in Twin Compared With Singleton Pregnancies. *Obstetrics and Gynecology*, 2019, 133 (6), pp.1141-1150. 10.1097/AOG.0000000000003261 . hal-04524835

HAL Id: hal-04524835

<https://hal.science/hal-04524835>

Submitted on 4 Apr 2024

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.

Severe Acute Maternal Morbidity in Twin Compared With Singleton Pregnancies

Authors:

Hugo Madar^{1,2}, MD, MPH; François Goffinet^{1,3}, MD, PhD; Aurélien Seco^{1,4}, MSc;

Patrick Rozenberg⁵, MD, MPH; Corinne Dupont^{6,7}, RM, PhD; Catherine Deneux-

Tharaux¹, MD, PhD on behalf of the EPIMOMS (EPIdémiologie de la MORbidité

Maternelle Sévère) Study Group*

Affiliations:

¹ INSERM U1153, Obstetrical, Perinatal and Pediatric Epidemiology (Epopé)

Research Team, Center for Epidemiology and Statistics Sorbonne Paris Cité

(CRESS), DHU Risks in Pregnancy, Paris Descartes University, Paris, France

² Department of Obstetrics and Gynecology, Bordeaux University Hospital,

Bordeaux, France

³ Department of Obstetrics and Gynecology, Cochin, Port-Royal Hospital, Assistance

Publique-Hôpitaux de Paris, Paris, France

⁴ URC-CIC Paris Descartes Necker-Cochin, AP-HP, Cochin Hospital, Paris, France

⁵ Department of Obstetrics and Gynecology, Intercommunal Poissy-St-Germain-en-

Laye Hospital, Poissy, France

⁶ Perinatal Aurore Network, Croix-Rousse Hospital, Lyon Civil Hospices, Lyon,

France

⁷ University Lyon, University Claude Bernard Lyon 1, Lyon, France

Corresponding author:

Catherine Deneux-Tharaux, MD, PhD

18-2218R1 Madar

2-7-19v2

2

26 INSERM U1153 – Équipe EPOPé

27 Maternité Port Royal, 53 avenue de l'observatoire

28 75014 Paris, France.

29 Tel: +33142345579 – Fax : +33143268979

30 E-mail address: catherine.deneux-tharaux@inserm.fr

31

32 *A list of members of the EPIMOMS Study Group is available in Appendix 1 online at

33 <http://links.lww.com/xxx>.

34

35 **Source of funding:** The EPIMOMS study was funded with support from the National
36 Research Agency (ANR) and the Ile de France Regional Health Agency (ARS). HM
37 received a training grant from the Aquitaine Regional Health Agency. The funders
38 had no role in the study design, data collection and analysis, decision to publish, or
39 preparation of the manuscript.

40

41 **Short title:** Twin Pregnancy and Severe Maternal Morbidity

42

43 **Acknowledgments:**

44 The authors thank the coordinators of the participating regional perinatal networks for their help in the
45 coordination of women's inclusion and data collection in their region: Alsace, Aurore, Auvergne,
46 Basse-Normandie, MYPA, NEF, Paris Nord, 92 nord, Lorraine; Chloé BARASINSKI, Sophie BEDEL,
47 Aline CLIN D'AMOUR, Laurent GAUCHER, Isabelle LECREFF, Blandine MASSON, Carole
48 RAMOUSSET, Mathias ROSSIGNOL, Zelda STEWART, Dalila TALAOURLAR, Yacine TOURE, and
49 Nicole WIRTH for their contribution to the implementation of the EPIMOMS study in their regions; the
50 obstetricians, midwives, and anesthetists who contributed to case identification and documentation in

51 their hospitals; and the research assistants who collected the data. The authors also thank Jo
52 Ann Cahn for editorial assistance.

53

54 Presented at the 38th Annual Pregnancy Meeting of the Society for Maternal and
55 Fetal Medicine (January 29-February 3, 2018), Dallas, TX.

56

57

58 ***Financial Disclosure***

59 *The authors did not report any potential conflicts of interest.*

60

61 *Each author has confirmed compliance with the journal's requirements for authorship.*

62

63 Word count (abstract without headlines): 309 words

64 Word count (main text): 3621 words

65 Tables to appear in the print issue: 4

66 Box to appear in the print issue: 2

67 Figures to appear in the print issue: 1

68 Appendix: 1 Text, 3 Tables and 1 Figure

18-2218R1 Madar

2-7-19v2

4

69 **Précis:** The risk of severe acute maternal morbidity is 4 times higher in twin than
70 singleton pregnancies.

71

ABSTRACT

Objective: To investigate the association between twin pregnancy and severe acute maternal morbidity, overall and by timing (before, during or after delivery) and underlying causal condition. A secondary objective was to explore the contribution of cesarean delivery as an intermediate factor in this association.

Methods: We conducted a cohort-nested case-control analysis from the EPIMOMS prospective study conducted in six French regions in 2012-2013 (N=182,309 deliveries). The case group comprised 2,500 women with severe acute maternal morbidity (defined by a national expert consensus process) occurring between 22 weeks of gestation and 42 days postpartum. A random sample of 3,650 women who gave birth without severe acute maternal morbidity made up the control group. The association between twin pregnancy and severe acute maternal morbidity was analyzed with multilevel multivariable logistic regression. The role of cesarean delivery as an intermediate factor between twin pregnancy and severe acute maternal morbidity was assessed by path analysis.

Results: The population-based incidence of severe acute maternal morbidity was 6.2% (n=197/3,202, 95%CI 5.3-7.1) in twin pregnancies, and 1.3% (n=2,303/179,107, 95%CI 1.2-1.3) in singleton pregnancies. After controlling for confounders, the risk of severe acute maternal morbidity was higher in twin than in singleton pregnancies (adjusted odds ratio [adjusted OR] 4.2, 95%CI 3.1-5.8), both antepartum and intra or postpartum, and regardless of the category of causal condition (severe hemorrhage, severe hypertensive complications, or other conditions). The association was also found for the most severe near-miss cases (adjusted OR 5.1, 95%CI 3.5-7.3). In path analysis, cesarean delivery mediated

97 20.6% (95%CI 12.9-28.2) of the total risk of intra or postpartum severe acute
98 maternal morbidity associated with twin pregnancy.

99 **Conclusion:** Compared to women with singleton pregnancies, women with twins
100 have a fourfold increased risk for severe maternal complications both before and
101 after delivery. About a fifth of the association between twin pregnancy and
102 intrapartum or postpartum severe acute maternal morbidity may be mediated by
103 cesarean delivery.

104

105 Introduction

106

107 The incidence of twin pregnancy has risen over the past 20 years, due mainly to
108 infertility treatments and older maternal age.¹⁻³ In 2016, the twin pregnancy rate was
109 around 1.8% in France and 1.7% in the United States.^{1, 4} Both neonatal and maternal
110 complications are more common with twins than singletons, including premature
111 birth, hypertensive disorders of pregnancy, obstetric hemorrhage and abnormal
112 placentation.⁵⁻⁹ However, our knowledge of the association of twins with maternal
113 severe health effects and organ dysfunction is incomplete. Most of the few previous
114 studies reporting an increased risk of severe maternal outcomes in twin pregnancies
115 have notable methodological limitations, including their analysis of retrospective or
116 administrative databases, failure to control for confounders, and use of an outcome
117 definition that is limited to selected obstetric complications and fails to take the
118 woman's health into account.¹⁰⁻¹⁴ A recent study conducted by the World Health
119 Organization (WHO) mostly in low or middle income countries reported a higher risk
120 of "maternal near-miss" events in twin pregnancies, but the generalizability of its
121 results for high-income countries remains controversial, given the contrasts in
122 practices and organization of care.^{12, 15} In addition, it seems important to
123 characterize intermediate factors that might lie on the causal pathway from twin
124 pregnancy to severe maternal morbidity. Literature about these potential
125 intermediate factors is even more limited, and route of delivery might be a major
126 candidate for such a factor, since cesarean deliveries are more frequent in twin
127 pregnancies and have been associated with a higher risk of severe maternal
128 morbidity than vaginal births.¹⁶⁻¹⁹ Our objective was to investigate the association
129 between twin pregnancy and severe acute maternal morbidity, overall and by timing

(ante partum or intra or post partum) and underlying causal condition. A secondary objective was to explore the contribution of cesarean delivery as an intermediate factor in this association.

Methods

This population-based, cohort-nested, case-control analysis used data from the EPIMOMS study, a prospective study specifically designed to study severe acute maternal morbidity and conducted in six French regions from May 2012 through November 2013.²⁰ The EPIMOMS study includes a standardized definition of severe acute maternal morbidity developed through a national Delphi formal expert consensus process and intended to characterize maternal complications with severe health effects and organ dysfunction. The EPIMOMS definition of severe acute maternal morbidity combines diagnoses (major obstetric bleeding, eclampsia, severe preeclampsia, pulmonary embolism, stroke, and psychiatric disorder), organ dysfunctions (cardiovascular, respiratory, renal, neurological, hepatic, and hematological), and interventions (intensive care admission and laparotomy after delivery) (definition detailed in Appendix 2, available online at <http://links.lww.com/xxx>).

Recruitment took place over a one-year period in each region at hospitals, with 119 maternity units and 136 intensive care units participating. They comprised 182,309 deliveries, approximately 20% of those in France during the study period, and the characteristics of both parturients and hospitals were similar to the national profile.²¹ Although all deliveries were counted, only minimal information was available for all,

including multiple or singleton status. For all those with severe acute maternal morbidity (Cases) and a random sample of those without (Controls) specific detailed information was collected. This design has the assets of a cohort (in particular no selection bias due to a lack of comparability of cases and controls since they are selected from the exactly same source population) while minimizing the number of women included and the related costs.

All women who experienced a severe acute maternal morbidity event between 22 weeks of gestation and 42 days postpartum were prospectively identified and included in EPIMOMS. The completeness of case identification was controlled by review of delivery logbooks, hospital discharge data, and laboratory files.

Concomitantly, at the end of the inclusion period, a 2% unmatched random sample of women who gave birth without severe acute maternal morbidity in the same regions during the same time period was selected from the maternity units' birth registers as the control group. In order to show an odds ratio of > 1.5 or < 0.67 for a factor with a prevalence of 5% or more among controls with $\alpha=0.05$ and $1-\beta=0.9$, 3,600 controls (or 2% of the cohort) were needed. For each maternity unit, 2% of their deliveries were selected as controls. Control women were women without severe acute maternal morbidity; this definition did not exclude non-severe maternal morbidity. The sampling method was to randomly select a number x between 1 and 50 and then to select 1 every 50 deliveries during the 1 year study period in each unit; in case this process selected a woman with SAMM, the delivery just before was selected as a control.

Data about women's social and demographic characteristics, preexisting medical and obstetric conditions, characteristics and complications of the current pregnancy and delivery, and details about the course and management of the severe acute

maternal morbidity were collected from medical records in which those items were prospectively recorded as they occurred. The data collection method was similar for women with severe acute maternal morbidity and control women and in all regions. Information was extracted from paper charts by research midwives trained for this study, and entered in a specific electronic report form developed for the study. In addition, for women with severe acute maternal morbidity, the criteria and causes of severe acute maternal morbidity were entered by the clinician in charge. Because the severe acute maternal morbidity case criteria, does not necessarily correspond directly to its cause, we also recorded the causal condition and clinical timing (antepartum, intrapartum or postpartum), as recorded prospectively by the clinician in charge.

For this study, we excluded triplet pregnancies because this subgroup is both likely to be at specific risk of severe acute maternal morbidity and too small to be distinguished in the analysis. We further excluded 30 women with significant obstetric data missing, most likely because they developed severe acute maternal morbidity due to a non-obstetric condition (trauma or psychiatric disorder) early in pregnancy and were then lost to follow-up (Figure 1).

The primary outcome was severe acute maternal morbidity, as a binary variable. Women who experienced more than one such event were counted once in this analysis; however we described the number of severe acute maternal morbidity events per woman. To isolate the most severe fraction of severe acute maternal morbidity cases, a secondary outcome was defined to include maternal near-misses as defined by World Health Organization¹⁵ (see criteria in Box 1); given the extreme

205 rarity of maternal deaths, they were included in this more severe “near-miss”
206 outcome and not isolated as a specific outcome; for brevity and clarity, this group will
207 be referred to as the “near miss” group in the manuscript.

208 The analysis of the association between twin pregnancy and severe acute maternal
209 morbidity considered the covariables listed in Box 2

210

211 “Near-miss” status, timing of severe acute maternal morbidity, and underlying
212 causal conditions were described among the cases according to twin or singleton
213 pregnancy status. For women who had several severe acute maternal morbidity
214 events, the timing of the first event was considered.

215

216 We compared the characteristics of cases and controls, based on Pearson’s chi-
217 square test or Fisher’s exact test for categorical variables, and Student’s t test or
218 Wilcoxon-Mann-Whitney test for quantitative variables, as appropriate. Statistical
219 significance was set at a two-tailed value of $P < .05$.

220

221 The association between twin pregnancy and severe acute maternal morbidity was
222 analyzed with multivariable multilevel logistic regression to take into account the
223 data’s hierarchical structure (women within maternity units). Causal assumptions
224 between twin pregnancy, severe acute maternal morbidity, and covariates were
225 represented with a directed acyclic graph (DAG) to depict the exposure-outcome
226 relations with confounding and intermediate factors (Appendix 3, available online at
227 <http://links.lww.com/xxx>). The DAG thus helped to select variables that are
228 confounders (ie, variables associated with both the exposure, which is twin
229 pregnancy, and the outcome of severe acute maternal morbidity and not on the

causal pathway between twin pregnancy and severe acute maternal morbidity) and those that do not qualify as confounders (especially intermediate factors).²² The main regression model included only strict confounders: maternal age, maternal country of birth, parity, and conception by IVF. Because the relation between severe acute maternal morbidity and maternal age (continuous variable) was not linear, this variable was transformed into second degree fractional polynomials. The only potential interaction considered clinically relevant was between twin pregnancy and maternal age and was not significant.

A sensitivity analysis used a regression model that included, in addition to the confounders of the main model, other variables that are risk factors for severe acute maternal morbidity but not associated with twin pregnancy (ie, single mother (used as a proxy for social vulnerability), body mass index, previous cesarean, preexisting medical condition, previous hypertensive disorder in pregnancy, and previous obstetric hemorrhage).

The same analysis strategy was used to assess the associations between twin pregnancy and each of the following specific categories of severe acute maternal morbidity: maternal “near-miss” events, the timing of severe acute maternal morbidity occurrence (antepartum and intra or postpartum), and the underlying causal conditions (severe obstetric hemorrhage, severe hypertensive complications, and all other underlying causal conditions).

The proportion of women with missing data for any covariate included in the main multivariable model ranged from 0% to 13.7%. There were 2227 (89.1%) cases and

255 3048 (83.5%) controls with no missing data for covariates included in the main
256 multivariable model. Characteristics of the women with full data were similar to those
257 with missing data (Appendix 4, available online at <http://links.lww.com/xxx>). We used
258 multiple imputation chained equations according to Rubin's rules to impute missing
259 data (20 data sets imputed). The results of the univariable and multivariable analysis
260 are presented with the imputed data. We also performed an analysis with the non-
261 imputed data.

262

263 A secondary analysis estimated the contribution of cesarean delivery (versus vaginal
264 delivery) as an intermediate factor in the association between twin pregnancy and
265 severe acute maternal morbidity by path analysis.²² The first step was to select a
266 relevant population to minimize the indication bias between cesarean delivery and
267 severe acute maternal morbidity, ie, the fact that some clinical situations will
268 influence both the mode of delivery, specifically the indication for cesarean, and the
269 risk of severe acute maternal morbidity, and can thus lead to incorrectly attributing a
270 risk present before the procedure to the cesarean. We therefore excluded women
271 with antepartum severe acute maternal morbidity (n=585), women in situations in
272 which one or the other mode of delivery is used systematically, either cesarean (for
273 fetal transverse position or unknown position (n=59) or for at least two previous
274 cesareans (n=97)) or vaginal (home births (n=10), medical termination of pregnancy
275 (n=7), in utero and intrapartum fetal deaths (n=40)), women with obstetric conditions
276 that developed during pregnancy, were symptomatic and present before labor but
277 without severe acute maternal morbidity at this stage, and responsible for a
278 postpartum severe acute maternal morbidity (for example gestational hypertension
279 or placenta praevia) (n=233), women with severe acute maternal morbidity during

280 labor that required an emergency cesarean (n=6) and women with unknown mode of
281 delivery (n=1). These exclusions left 1,462 women with intrapartum or postpartum
282 severe acute maternal morbidity including 1,253 (85.7%) without missing data for the
283 variables included in this secondary model (see below), which were the cases used
284 for this secondary analysis. Applying similar exclusion criteria to the control group
285 resulted in using 3,464 women without severe acute maternal morbidity, including
286 2,816 (81.3%) without missing data, which were the controls for this secondary
287 analysis.

288 Following the method proposed by Erikson et al. and generalized by Buis,^{23, 24} the
289 total effect of twin pregnancy on severe acute maternal morbidity was decomposed
290 into an indirect effect mediated by cesarean delivery and a direct (or residual) effect
291 not mediated by cesarean delivery. This method of analysis is based on a
292 counterfactual approach to causality and confounding that can be formulated as the
293 answer to the following question: "what would the risk of severe acute maternal
294 morbidity associated with twin pregnancy be if twin pregnancies had the same
295 probability of cesarean delivery as singleton pregnancies?" The indirect effect of twin
296 pregnancy on the risk of severe acute maternal morbidity, mediated by cesarean
297 delivery, was calculated from the regression coefficients obtained through logistic
298 regression models, adjusted for the same covariates as the main model but also for
299 confounders in the association between mode of delivery and severe acute maternal
300 morbidity (see Appendix 3). This indirect effect was expressed as a percentage of
301 the total effect.

302

303 At the conventional 2-tailed significance level of $\alpha=0.05$, with a twin pregnancy
304 prevalence of 1.6%, the available number of cases and controls provided a statistical

power of 80% to show an odds ratio greater than or equal to 1.7 quantifying the association between twin pregnancy and severe acute maternal morbidity. STATA 13 software (StataCorp LP, College Station, TX) was used for the descriptive and multivariable analyses.

The *Commission Nationale de l'Informatique et des Libertés* (CNIL, no 912210), the French data protection agency, approved the EPIMOMS study.

Results

The total cohort included 182,309 women of whom 1.4% (95%CI 1.3-1.4) (n=2,540) had severe acute maternal morbidity. Among 3,202 twins, severe acute maternal morbidity occurred in 197 (6.2%, 95%CI 5.3-7.1%) and in 2,303 of the 179,007 singletons (1.3%, 95%CI 1.2-1.3%). Our analysis included 2,500 severe acute maternal morbidity cases and 3,650 controls. Most cases of severe acute maternal morbidity occurred intra or postpartum (76.6%, n=1,915/2,500). The two most common underlying causal conditions of severe acute maternal morbidity were severe obstetric hemorrhage (65.6%, n=1,641/2,500) and severe hypertensive complications (19.5%, n=488/2,500) (Table 1). Maternal near-misses accounted for 37.4% of severe acute maternal morbidity cases (n=934/2,500) including 13 maternal deaths all of which occurred in singletons. The distribution of the timing, underlying causal conditions and severity of severe acute maternal morbidity did not differ significantly in twin and singleton pregnancies (Appendix 5, available online at <http://links.lww.com/xxx>).

330

331 Among cases, 7.9% (197/2,500) were twins and among controls, twins were present
332 in 1.6% (59/3,650) (unadjusted OR 4.7, 95% CI 3.5-6.4) (Tables 2 and 3). Compared
333 with controls, women who experienced a severe acute maternal morbidity event
334 were older; they were more often born in sub-Saharan Africa and “other” countries,
335 nulliparous, and pregnant by IVF. They also had a higher frequency of preexisting
336 medical conditions, history of abdominopelvic surgery, obstetric complications,
337 previous cesarean deliveries, and preterm and cesarean deliveries (Table 2).

338

339 In the multivariable analysis, compared with singleton pregnancies, twin pregnancies
340 were at higher risk of severe acute maternal morbidity (adjusted OR 4.2, 95% CI 3.1-
341 5.8), both antepartum (adjusted OR 4.1, 95% CI 2.5-6.6) and intra or postpartum
342 (adjusted OR 4.2, 95% CI 3.1-5.9), from severe obstetric hemorrhage (adjusted OR
343 4.8, 95% CI 3.5-6.7), severe hypertensive complications (adjusted OR 4.8, 95% CI
344 2.9-8.0), and other underlying causal conditions (adjusted OR 3.0, 95% CI 1.7-5.2),
345 and of near-misses (adjusted OR 5.1, 95% CI 3.5-7.3) (Table 3). The sensitivity
346 analysis adjusted for strict confounders and other risk factors for severe acute
347 maternal morbidity yielded similar results (Table 3), as did the analyses with non-
348 imputed data (results not shown).

349

350 In the population selected for the secondary analysis, the cesarean rate among
351 controls was 57.7% for twin pregnancies and 17.6% for singleton pregnancies
352 ($P<0.001$); among cases, it was respectively 71.7% and 34.1% ($P<0.001$). Table 4
353 shows the results of the path analysis to assess the contribution of cesarean delivery
354 as an intermediate factor in the relation between twin pregnancy and intra or

postpartum severe acute maternal morbidity. In this secondary analysis, the association between twin pregnancy and intra or postpartum severe acute maternal morbidity was similar to that in the main analysis (crude OR 5.9, 95% CI 4.2-8.2; and adjusted OR 5.2, 95% CI 3.5-7.7). Therefore, 20.6% (95% CI 12.9-28.2%) of the total risk of intra or postpartum severe acute maternal morbidity associated with twin pregnancy was mediated by cesarean delivery.

Discussion

We found a strong association between twin pregnancy and severe acute maternal morbidity: the risk was four times higher than for singleton pregnancy after controlling for identified confounders. This excess risk was also found for maternal near-misses and before, during or after delivery. Path analysis taking into account the potential indication bias suggests that about a fifth of the association between twin pregnancy and intra or postpartum severe acute maternal morbidity was mediated by cesarean delivery; in other words, if twin pregnancies had the same probability of cesarean delivery as singleton pregnancies, the association found between twin pregnancy and intra or postpartum severe acute maternal morbidity would be reduced by a fifth.

This population-based design allowed us to take into account the diversity of women and practices that can impact severe maternal morbidity. The national Delphi-Rand formalized process produced a consensual and comprehensive definition of severe acute maternal morbidity based on specific criteria for severe health effects and organ dysfunction. The prospective identification of cases was as exhaustive as

possible; all severe acute maternal morbidity events corresponding to this precise definition were identified during the period and checked afterwards. The detailed data of maternal and severe acute maternal morbidity characteristics made it possible to apply the WHO definition of "maternal near-miss" to our population and to distinguish severe acute maternal morbidity by clinical timing, which has practical implications, and underlying causal condition, as well as to consider a large number of confounders. Path analysis furnished additional information about the potential intermediate role of cesarean delivery in the association between twin pregnancy and intra or postpartum severe acute maternal morbidity. Our special focus on controlling confounding by indication for this secondary analysis minimized this bias, which often impairs analyses of the adverse consequences of cesarean deliveries.

The external validity of this study may be limited by the participating population identified from six French regions. Although this was not a random sample of French parturients, the characteristics of women and maternity units in this large source population (one fifth of national deliveries) were similar to the national profile.²¹ Nevertheless, obstetric practices and the management of twin pregnancies vary across countries, and these differences may limit the generalizability of our results.

Without distinguishing the level of severity of maternal complications and based on international retrospective hospital data, Conde-Agudelo et al. reported a 2-fold adjusted (for maternal age and parity) risk of hypertensive disorder in pregnancy and postpartum hemorrhage for twin pregnancies.¹⁰ Studying 1995-2000 birth certificates in the United States, Luke et al. found a significant crude association between twin pregnancies and adverse obstetric outcomes, but did not distinguish severe maternal

405 morbidity.¹¹ The analysis by Walker et al. of 1984-2000 Canadian data showed a
406 higher risk of adverse obstetric outcomes in twin pregnancies, without adjustment for
407 potential confounders.¹³ The validity of the data provided by hospital-based
408 retrospective studies and administrative databases remains questionable, and to our
409 knowledge, only a few observational prospective studies were designed to study
410 severe maternal morbidity. In a cohort of 2,552 cases of severe maternal morbid
411 events, including 202 twin pregnancies in 2004-2006, Witteveen et al. in the
412 Netherlands showed a significant association between twin pregnancy and severe
413 maternal morbidity (OR 4.3, 95% CI 3.7-5.0), without adjustment for potential
414 confounding factors.¹⁴ Furthermore, their definition of severe maternal morbidity was
415 restricted to certain components (intensive care unit admission, uterine rupture,
416 eclampsia, severe obstetric hemorrhage). In a prospective international study
417 conducted by WHO in 2010-2011, twin pregnancy was significantly associated with
418 "maternal near-miss" (OR adjusted for the country of birth 3.03, 95% CI 2.39-
419 3.85).¹² After adjustment for maternal age, parity, medical conditions, obstetric
420 complications, and mode of delivery, but restricted to low and middle income
421 countries, Vogel et al. found an adjusted OR of severe adverse maternal outcome
422 (including death) of 1.85 (95% CI 1.60-2.14) in twin pregnancies.²⁵ We were able to
423 apply the WHO "maternal near-miss" definition to our cases and found crude and
424 adjusted ORs of "maternal near-miss" or death in twin pregnancies of 5.7 (95% CI
425 4.0-8.1) and 5.1 (95% CI 3.5-7.3), respectively. These differences may be explained
426 by the dominant participation of medium to low-income countries, with their higher
427 levels of risk, including for the reference group of singleton pregnancies.

Results of the analysis of the risk of severe acute maternal morbidity by timing and by underlying causal condition are informative for clinical practice. Twin delivery is known to be at a higher risk of postpartum hemorrhage, and our analysis confirmed and quantified this association for the most severe hemorrhages and after adequate controlling for confounders. However, we showed that the risk of severe acute maternal morbidity in women with twin pregnancies is also markedly higher in the antepartum period and for underlying causal conditions other than severe obstetric hemorrhage. These results should encourage obstetricians to provide women carrying twins with close medical monitoring during prenatal care –an example may be the detection of antepartum anemia with iron supplementation to prevent severe maternal anemia post-delivery- and to plan the delivery in a maternity unit appropriate for these maternal risks –in particular with on-site extensive access to blood products, adult intensive care unit, and surgical expertise. This finding also underlines the potential consequences of infertility treatments, including multiple embryo transfer in IVF, an important provider of twin pregnancies² (one quarter of twin pregnancies in France in 2010³).

We found that about a fifth of the association between twin pregnancy and intra or postpartum severe acute maternal morbidity may be mediated by cesarean delivery. Although we did not differentiate cesarean by timing in this analysis, this finding provides further support to the recommendation to limit the use of cesareans for twin deliveries to situations where it is clearly medically indicated.²⁶ In our study, more than half of control women with twin pregnancy, and about three quarters of cases with twin pregnancy, delivered by cesarean. Increasing the rate of vaginal deliveries

453 in twin pregnancies, unless there is an obstetric or fetal indication otherwise, may
454 decrease the rate of severe acute maternal morbidity in these women.

455

456 **References:**

457

458 1. Blondel B, Coulm B, Bonnet C, Goffinet F, Le Ray C, National Coordination Group
459 of the National Perinatal Surveys. Trends in perinatal health in metropolitan France
460 from 1995 to 2016: Results from the French National Perinatal Surveys. J Gynecol
461 Obstet Hum Reprod 2017 Dec;46(10):701-13.

462 2. Kulkarni AD, Jamieson DJ, Jones HW, Jr., Kissin DM, Gallo MF, Macaluso M, et
463 al. Fertility treatments and multiple births in the United States. The New England
464 journal of medicine 2013 Dec 5;369(23):2218-25.

465 3. Prunet C, Goffinet F, Blondel B. Medical care and perinatal health in twin
466 pregnancies: situation in 2010 and recent trends in France. Journal de gynecologie,
467 obstetrique et biologie de la reproduction 2015 Feb;44(2):184-93.

468 4. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK, Drake P. Births: Final Data
469 for 2016. Natl Vital Stat Rep 2018 Jan;67(1):1-55.

470 5. Gyamfi C, Stone J, Eddleman KA. Maternal complications of multifetal pregnancy.
471 Clinics in perinatology 2005 Jun;32(2):431-42, vii.

472 6. Senat MV, Ancel PY, Bouvier-Colle MH, Breart G. How does multiple pregnancy
473 affect maternal mortality and morbidity? Clinical obstetrics and gynecology 1998
474 Mar;41(1):78-83.

475 7. Young BC, Wylie BJ. Effects of twin gestation on maternal morbidity. Seminars in
476 perinatology 2012 Jun;36(3):162-8.

- 477 8. Heino A, Gissler M, Hindori-Mohangoo AD, Blondel B, Klungsoyr K, Verdenik I, et
478 al. Variations in Multiple Birth Rates and Impact on Perinatal Outcomes in Europe.
479 PloS one 2016;11(3):e0149252.
- 480 9. Rao A, Sairam S, Shehata H. Obstetric complications of twin pregnancies. Best
481 practice & research Clinical obstetrics & gynaecology 2004 Aug;18(4):557-76.
- 482 10. Conde-Agudelo A, Belizan JM, Lindmark G. Maternal morbidity and mortality
483 associated with multiple gestations. Obstetrics and gynecology 2000 Jun;95(6 Pt
484 1):899-904.
- 485 11. Luke B, Brown MB. Contemporary risks of maternal morbidity and adverse
486 outcomes with increasing maternal age and plurality. Fertility and sterility 2007
487 Aug;88(2):283-93.
- 488 12. Santana DS, Cecatti JG, Surita FG, Silveira C, Costa ML, Souza JP, et al. Twin
489 Pregnancy and Severe Maternal Outcomes: The World Health Organization
490 Multicountry Survey on Maternal and Newborn Health. Obstetrics and gynecology
491 2016 Apr;127(4):631-41.
- 492 13. Walker MC, Murphy KE, Pan S, Yang Q, Wen SW. Adverse maternal outcomes
493 in multifetal pregnancies. BJOG : an international journal of obstetrics and
494 gynaecology 2004 Nov;111(11):1294-6.
- 495 14. Witteveen T, Van Den Akker T, Zwart JJ, Bloemenkamp KW, Van Roosmalen J.
496 Severe acute maternal morbidity in multiple pregnancies: a nationwide cohort study.
497 American journal of obstetrics and gynecology 2016 May;214(5):641 e1- e10.
- 498 15. Say L, Souza JP, Pattinson RC, W. H. O. working group on Maternal Mortality
499 Morbidity classifications. Maternal near miss--towards a standard tool for monitoring
500 quality of maternal health care. Best practice & research Clinical obstetrics &
501 gynaecology 2009 Jun;23(3):287-96.

- 502 16. Barrett JF, Hannah ME, Hutton EK, Willan AR, Allen AC, Armson BA, et al. A
503 randomized trial of planned cesarean or vaginal delivery for twin pregnancy. The
504 New England journal of medicine 2013 Oct 3;369(14):1295-305.
- 505 17. Hutton EK, Hannah ME, Ross S, Joseph KS, Ohlsson A, Asztalos EV, et al.
506 Maternal outcomes at 3 months after planned caesarean section versus planned
507 vaginal birth for twin pregnancies in the Twin Birth Study: a randomised controlled
508 trial. BJOG : an international journal of obstetrics and gynaecology 2015
509 Nov;122(12):1653-62.
- 510 18. Liu S, Liston RM, Joseph KS, Heaman M, Sauve R, Kramer MS, et al. Maternal
511 mortality and severe morbidity associated with low-risk planned cesarean delivery
512 versus planned vaginal delivery at term. CMAJ 2007 Feb 13;176(4):455-60.
- 513 19. Villar J, Carroli G, Zavaleta N, Donner A, Wojdyla D, Faundes A, et al. Maternal
514 and neonatal individual risks and benefits associated with caesarean delivery:
515 multicentre prospective study. Bmj 2007 Nov 17;335(7628):1025.
- 516 20. Siddiqui A, Azria E, Howell EA, Deneux-Tharaux C, Epimoms Study Group.
517 Associations between maternal obesity and severe maternal morbidity: Findings
518 from the French EPIMOMS population-based study. Paediatric and perinatal
519 epidemiology 2018 Oct 17;doi:10.1111/ppe.12522.
- 520 21. Blondel B, Lelong N, Kermarrec M, Goffinet F, National Coordination Group of
521 the National Perinatal Surveys. Trends in perinatal health in France from 1995 to
522 2010. Results from the French National Perinatal Surveys. Journal de Gynécologie
523 Obstétrique et Biologie de la Reproduction 2012;41(4):e1-e15.
- 524 22. Ananth CV, Schisterman EF. Confounding, causality, and confusion: the role of
525 intermediate variables in interpreting observational studies in obstetrics. American
526 journal of obstetrics and gynecology 2017 Aug;217(2):167-75.

- 527 23. Buis ML. Direct and indirect effects in a logit model. Stata J 2010
528 Winter;10(1):11-29.
- 529 24. Erikson R, Goldthorpe JH, Jackson M, Yaish M, Cox DR. On class differentials in
530 educational attainment. Proceedings of the National Academy of Sciences of the
531 United States of America 2005 Jul 05;102(27):9730-3.
- 532 25. Vogel JP, Torloni MR, Seuc A, Betran AP, Widmer M, Souza JP, et al. Maternal
533 and perinatal outcomes of twin pregnancy in 23 low- and middle-income countries.
534 PloS one 2013;8(8):e70549.
- 535 26. Korb D, Deneux-Tharaux C, Seco A, Goffinet F, Schmitz T, JUmeaux MODe
536 d'Accouchement study group, et al. Risk of Severe Acute Maternal Morbidity
537 According to Planned Mode of Delivery in Twin Pregnancies. Obstetrics and
538 gynecology 2018 Sep;132(3):647-55.

540 **Table 1.** Characteristics of severe acute maternal morbidity among cases

Categories of Severe Acute Maternal Morbidity	Women with Severe Acute Maternal Morbidity	
	N = 2500	(%)
Timing		
Antepartum	585	(23.4)
Intra or postpartum	1915	(76.6)
Underlying causal condition*		
Obstetric hemorrhage	1641	(65.6)
Including*:		
Blood loss \geq 1500 mL	956	(38.2)
Transfusion \geq 4 units of red blood cells	444	(17.8)
Conservative surgery or embolization	437	(17.5)
Hysterectomy following hemorrhage	104	(4.2)
Disseminated intravascular coagulation	276	(11.0)
Acute postpartum anemia with hemoglobin < 7 g/dL in the absence of chronic anemia	808	(32.3)
Hypertensive complications [†]	488	(19.5)
Including*:		
Severe preeclampsia	364	(14.6)
Eclampsia	51	(2.0)
Severe HELLP syndrome	174	(7.0)
Severe psychiatric disorder	95	(3.8)
Decompensation of preexisting condition	93	(3.7)

Sepsis	52	(2.1)
Pulmonary embolism	39	(1.6)
Amniotic fluid embolism	14	(0.6)
Other	247	(9.9)
Severity		
Maternal near-miss [‡]	934	(37.4)
Not maternal near-miss	1566	(62.6)
Number of Severe Acute Maternal Morbidity events:		
1	1649	(66.0)
2	551	(22.0)
≥ 3	300	(12.0)

541 *Data are n (%)*

542 *HELLP syndrome: hemolysis, elevated liver enzymes, and low platelet count*
543 *syndrome*

544 ** Non-exclusive categorization*

545 *† Severe preeclampsia, HELLP syndrome, eclampsia, placental abruption with*
546 *hypertensive disorder*

547 *‡ According to WHO definition (see Box 1) and including maternal deaths*

548 **Table 2.** Characteristics of women with severe acute maternal morbidity: cases and
 549 control women

Characteristics of women	severe acute		CONTROLS		p
	maternal				
	morbidity cases		N = 3650		
	N = 2500				
Main exposure					
Twin pregnancy	197	(7.9)	59	(1.6)	< 0.001
Maternal characteristics					
Age (y)*	31.2	(±5.6)	30.5	(±5.2)	< 0.001
Country of birth					< 0.001
France	1563	(69.7)	2313	(75.5)	
Other Europe	68	(3.0)	111	(3.6)	
North Africa	229	(10.2)	316	(10.3)	
Sub-Saharan Africa	243	(10.8)	173	(5.6)	
Other	141	(6.3)	150	(4.9)	
Single mother	155	(6.7)	135	(4.0)	< 0.001
BMI					< 0.001
< 18.5	167	(7.1)	261	(7.4)	

18-2218R1 Madar
2-7-19v2
28

18.5-24.9	1346	(57.4)	2137	(60.8)	
25.0-29.9	473	(20.2)	724	(20.6)	
≥ 30	357	(15.2)	395	(11.2)	
Preexisting medical condition[†]	371	(14.9)	274	(7.5)	< 0.001
History of abdominopelvic surgery	171	(6.9)	150	(4.1)	< 0.001
Parity					< 0.001
Nulliparous	1229	(49.6)	1517	(41.8)	
Parous	1247	(50.4)	2111	(58.2)	
Previous cesarean delivery	437	(17.7)	441	(12.3)	< 0.001
Previous obstetric hemorrhage	113	(4.5)	83	(2.3)	< 0.001
Previous hypertensive disorder in pregnancy	137	(5.5)	97	(2.7)	< 0.001
<hr/> Pregnancy <hr/>					
In vitro fertilization	146	(5.9)	76	(2.1)	< 0.001
Abnormal placentation	144	(5.8)	25	(0.7)	< 0.001
Third-trimester anemia	616	(26.6)	555	(16.6)	< 0.001

Delivery

Gestational age at delivery[‡] (weeks) 38.9 (35.9-40.3) 39.6 (38.7-40.6) < 0.001

Mode of delivery < 0.001

Spontaneous vaginal 818 (32.9) 2456 (67.3)

Operative vaginal 334 (13.4) 450 (12.3)

Antepartum cesarean 892 (35.9) 386 (10.6)

Intrapartum cesarean 442 (17.8) 357 (9.8)

Data are n (%) unless otherwise specified

BMI: body mass index

** Mean (±sd)*

† Chronic hypertension, diabetes, dyslipidemia, constitutional bleeding disorders, asthma, allergy, psychiatric disorders, thromboembolic disease, stroke, transient ischemic attack, coronary heart disease, severe trauma, heart disease, epilepsy, hemoglobinopathy, hepatopathy, thyroid dysfunction, systemic lupus erythematosus, autoimmune disease, inflammatory bowel disease, nephropathy, cancer, myasthenia gravis, myopathy, multiple sclerosis, respiratory disease

‡ Median (interquartile range)

560 **Table 3.** Association between twin pregnancy and severe acute maternal morbidity

Categories of severe acute maternal morbidity	Univariable	Multivariable	Sensitivity analysis
	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	Adjusted OR† (95% CI)
Severe acute maternal morbidity‡	4.7 (3.5-6.4)	4.2 (3.1-5.8)	4.4 (3.2-6.1)
Near-miss§	5.7 (4.0-8.1)	5.1 (3.5-7.3)	5.4 (3.7-7.9)
By timing:			
Antepartum severe acute maternal morbidity	4.1 (2.6-6.4)	4.1 (2.5-6.6)	4.6 (2.8-7.6)
Intra or postpartum severe acute maternal morbidity	4.9 (3.6-6.7)	4.2 (3.1-5.9)	4.5 (3.2-6.2)
By underlying causal condition:			
Severe obstetric hemorrhage	5.7 (4.2-7.9)	4.8 (3.5-6.7)	5.1 (3.6-7.1)
Severe hypertensive complications	4.6 (2.9-7.5)	4.8 (2.9-8.0)	6.1 (3.7-10.3)
Other underlying causal conditions	3.0 (1.8-5.1)	3.0 (1.7-5.2)	3.0 (1.7-5.3)

561 *Multilevel logistic regression and multiple imputation*562 *Reference: singleton pregnancy*563 *OR: odds ratio*564 *CI: confidence interval*

565 * Logistic regression model including only strict confounders: maternal age, maternal
566 country of birth, parity, and conception by in vitro fertilization

567 † Logistic regression model including confounders and other risk factors for severe
568 acute maternal morbidity: maternal age, maternal country of birth, parity, conception
569 by in vitro fertilization, single mother, body mass index, previous cesarean,
570 preexisting medical condition, previous hypertensive disorder in pregnancy, previous
571 obstetric hemorrhage

572 ‡ 2,500 severe acute maternal morbidity cases and 3,650 controls

573 § According to WHO definition (see Box 1) and including maternal deaths, 934
574 maternal near-misses and 3,650 controls

575 || 585 cases of antepartum severe acute maternal morbidity, 1,915 cases of intra or
576 postpartum severe acute maternal morbidity, 1,641 cases of severe obstetric
577 hemorrhage, 488 cases of severe hypertensive complications, 429 cases of other
578 underlying causal conditions and 3,650 controls

579 **Table 4.** Estimation of the contribution of cesarean delivery as an intermediate factor
 580 in the relation between twin pregnancy and intra or postpartum severe acute
 581 maternal morbidity , by path analysis*

Effect of Twin Pregnancy	severe acute maternal morbidity
	Adjusted OR [†] (95% CI)
Total effect	5.2 (3.5-7.7)
Indirect effect mediated by cesarean	1.4 (1.3-1.5)
Residual effect not mediated by cesarean	3.7 (2.5-5.5)
% Indirect effect[‡]	20.6 (12.9-28.2)

582 *OR: odds ratio*

583 *CI: confidence interval*

584 * *Decomposition of the total effect of twin pregnancy on the odds of severe acute*
 585 *maternal morbidity intra or postpartum into its “indirect” (mediated by cesarean*
 586 *delivery) and “residual direct” components; no multiple imputation, 1,253 cases of*
 587 *intra or postpartum severe acute maternal morbidity and 2,816 controls without*
 588 *missing data for covariables*

589 [†] *Covariables: maternal age, maternal country of birth, parity, conception by in vitro*
 590 *fertilization, body mass index, previous cesarean, preexisting medical condition,*
 591 *obstetric complications (hypertensive disorder in pregnancy and abnormal*
 592 *placentation)*

593 [‡] *Estimation from regression coefficients*

594

Box 1. World Health Organization (WHO) maternal near-miss criteria

Cardiovascular dysfunction	Shock
	Cardiac arrest (absence of pulse or heart beat and loss of consciousness)
	Use of continuous vasoactive drugs
	Cardiopulmonary resuscitation
	Severe hypoperfusion (lactate > 5mmol/L or > 45 mg/dL)
	Severe acidosis (pH < 7.1)
Respiratory dysfunction	Acute cyanosis
	Gasping*
	Severe tachypnea (respiratory rate > 40 breaths per minute)
	Severe bradypnea (respiratory rate < 6 breaths per minute)
	Intubation and ventilation (for ≥ 60 minutes*) not related to anesthesia
	Severe hypoxemia (O ₂ saturation < 90% (for ≥ 60 minutes*) or PaO ₂ /FiO ₂ < 200 mmHg)
Renal dysfunction	Oliguria non-responsive to fluids or diuretics
	Dialysis for acute renal failure
	Severe acute azotemia (creatinine ≥ 300 µmol/L or ≥ 3.5 mg/dL)
Hematological dysfunction	Failure to form clots
	Massive transfusion of blood or red cells (≥ 5 units)
	Severe acute thrombocytopenia (< 50,000 platelets/mL)

Hepatic dysfunction	Jaundice in the presence of preeclampsia
	Severe acute hyperbilirubinemia (bilirubin > 100 µmol/L or > 6.0 mg/dL)
Neurological dysfunction	Prolonged unconsciousness (lasting ≥ 12 hours*) or coma (including metabolic coma)
	Stroke
	Uncontrollable fit or Epileptic status
	Total paralysis
Uterine dysfunction	Uterine hemorrhage or infection leading to hysterectomy

596 Data from Say L, Souza JP, Pattinson RC, W H O working group on Maternal
 597 Mortality Morbidity classifications. Maternal near miss--towards a standard tool for
 598 monitoring quality of maternal health care. Best Pract Res Clin Obstet Gynaecol
 599 2009;23):287–96.

600 * Data not available in the EPIMOMS study: gasping, duration of intubation and
 601 ventilation, duration of hypoxemia and duration of prolonged unconsciousness

602

603 **Box 2.** Covariables considered in the analysis of the association between twin
 604 pregnancy and severe acute maternal morbidity

Maternal characteristics	<p>Age (continuous variable, in years)</p> <p>Country or birth (France, other Europe, North Africa, sub-Saharan Africa, others)</p> <p>Single mother</p> <p>Body mass index (underweight < 18.5, normal 18.5-24.9, overweight 25.0-29.9, obese ≥ 30 kg/m²)</p> <p>Preexisting medical condition (binary variable defined as at least one of the following conditions: cardiovascular disease, respiratory disease, stroke, bleeding disorder, thromboembolic disease, hemoglobinopathy, thyroid dysfunction, autoimmune disease, gastrointestinal disease, nephropathy, cancer, epilepsy, or psychiatric disorder)</p> <p>History of abdominopelvic surgery</p> <p>Parity (nulliparous or parous)</p> <p>Previous cesarean delivery</p> <p>Previous obstetric hemorrhage</p> <p>Previous hypertensive disorder in pregnancy</p>
Pregnancy characteristics	<p>Conception by in vitro fertilization</p> <p>Abnormal placentation</p> <p>Hypertensive disorder (eg, gestational hypertension or non-severe preeclampsia)</p> <p>Third-trimester anemia, defined as a hemoglobin level less than 11 g/dL</p>
Delivery characteristics	<p>Gestational age at delivery</p> <p>Mode of delivery (spontaneous vaginal, operative vaginal, antepartum cesarean, intrapartum cesarean)</p>

606 **Figure legends**

607

608 **Figure 1.** Flowchart of women included in the study (*SAMM: severe acute maternal*
609 *morbidity*)

610

611

612

613

614

615