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TITLE PAGE

Lower gestational age is associated with severe maternal morbidity of preterm cesarean delivery

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Short title:

Preterm cesarean and severe maternal morbidity

Lower gestational age is associated with severe maternal morbidity of preterm cesarean delivery

Abstract

Objective

To evaluate whether gestational age was associated with the severe maternal morbidity (SMM) of preterm cesarean delivery between 22 and 34 weeks of gestation (weeks).

Material and Methods

We performed an observational retrospective cohort study in two tertiary university hospitals in 2018. We included all mothers of preterm infants born by caesarean delivery between 22 and 34 weeks, excluding mothers with multiple births greater than two, with pregnancy terminations or stillbirths, and who died unrelated to obstetrical causes. The principal endpoint, SMM, was a composite outcome (classical uterine incision, postpartum hemorrhage defined by blood loss ≥ 500 mL, blood transfusion, any injury to adjacent organs, unplanned procedure/need for reintervention, Intensive Care Unit (ICU) stay longer than 24 hours, postpartum fever, and/or death).

Results

Among the 252 women, SMM occurred in 89 (35.3%) cases. After multivariate analysis, gestational age was independently associated with SMM (adjusted Odds Ratio [aOR] 0.87; 95% Confidence Interval [CI] 0.78-0.97). The other variables statistically associated with SMM were type of pregnancy with a negative association with twin pregnancy (aOR, 0.44; 95% CI, 0.20-0.93) and a positive association with general anesthesia (aOR, 2.52; 95% CI, 1.25-5.13). A sensitivity analysis was performed and found an association, at the limit of significance, between gestational age < 28 weeks and SMM (aOR, 1.80; 95% CI, 0.99-3.27, $p = 0.05$).

26 ***Conclusion***

27 Lower gestational age was associated with the risk of SMM for preterm cesarean delivery
28 between 22 and 34 weeks. Obstetricians should integrate this knowledge into their shared
29 decision-making processes with parents.

30 ***Key words***

31 Cesarean delivery, gestational age, prematurity, severe maternal morbidity, shared decision-
32 making

Introduction

The survival of preterm infants born between 22 and 28 weeks of gestation (weeks) has increased worldwide in the past few decades.¹⁻³ In France, a national population-based cohort study “EPIPAGE 2” reported a 14.4% increase in global neonatal survival without adverse outcomes between 1997 and 2011.⁴

The improvement in the survival of these extremely preterm infants is related to the development of neonatal proactive management as well as active antenatal care, such as caesarean delivery in the case of fetal indications.^{5,6} Preterm caesarean delivery rates have regularly increased, particularly before 26 weeks.^{1,2,7,8} However, European and American cohorts of preterm infants reported variable rates of caesarean delivery before 26 weeks.^{1,2,4,6,7} These heterogeneous care practices can be observed across and within countries⁵ and can be associated with disagreements in team care.⁹ A shared decision-making process is essential in situations at risk of extremely preterm delivery and should take into account available data regarding neonatal and maternal morbidity. Many studies have reported on neonatal morbidity in relation to the mode of delivery, but there is currently a paucity of data regarding maternal morbidity in relation to preterm caesarean delivery.¹⁰⁻¹³ In the case of term delivery, a severe maternal morbidity (SMM) associated with caesarean delivery is higher compared to SMM after vaginal delivery.¹⁴⁻¹⁶ Few studies have assessed the SMM of extremely preterm caesarean delivery as well as the association between gestational age and SMM.^{17,18} We have recently reported a secondary analysis of a population-based cohort study, demonstrating that mothers undergoing a caesarean delivery before 26 weeks experienced more than a two-fold increase in the risk of SMM compared with those undergoing a caesarean delivery between 26 and 34 weeks.¹⁹ The strength of this previous study was its specific prospective population-based cohort design, with its main limitation being the evaluation of SMM (defined as the occurrence of severe postpartum hemorrhage defined by the use of a blood transfusion,

58 intensive care unit admission, or death) using available maternal variables from this cohort of
59 preterm infants.
60 To confirm the hypothesis that lower gestational age is associated with a greater risk of SMM
61 of preterm caesarean delivery, we performed as a sensitivity analysis, a recent retrospective
62 cohort study in local tertiary care centers.

Material and Methods

Study population and setting

We performed an observational retrospective cohort study in two tertiary university hospitals in Marseille, France between January and December 2018.

We included all the mothers of preterm infants born by caesarean delivery between 22 and 34 weeks, excluding mothers with multiple births greater than two, mothers with a history of pregnancy terminations or stillbirths, and case of maternal death unrelated to an obstetrical cause.

Data collection

Maternal, obstetrical, and neonatal data were collected retrospectively from each mother's and infants' electronic medical files.

D.S. entered the data and the accuracy of the database was validated by J.B. and N.R..

Outcomes and studied factors

The principal endpoint, Severe Maternal Morbidity (SMM), was a composite outcome defined as the occurrence of at least one of the following complications:

- classical uterine incision (referring to an incision in the upper uterine segment and because classical incision leads to a caesarean delivery upon the next pregnancy and therefore increases the global maternal morbidity rate);
- postpartum hemorrhage defined as blood loss ≥ 500 mL (as defined by the World Health Organization and French clinical guidelines ²⁰);
- blood transfusion;
- any injury of adjacent organs (gastrointestinal, urological, or vascular),
- unplanned procedure/need for reintervention;

- Intensive Care Unit (ICU) stay longer than 24 hours in duration;
- postpartum fever;
- and/or death.

This composite endpoint was chosen as a synthesis of prior definitions of severe maternal morbidity in these clinical situations literature and depending on available data during the stay of the mother.^{18,19,21–23}

The main studied factor was gestational age at caesarean delivery. As a sensitivity analysis, gestational age was also studied as a binary variable with the threshold of 26 and 28 weeks, the usual thresholds defining extreme and very high prematurity, respectively. Gestational age was routinely determined by the first trimester ultrasound and verified before any extremely early caesarean delivery. If the first trimester ultrasound was not performed (less than 5% of the women), gestational age was best estimated based on the last menstrual period and its consistency with the measured head circumference of the earliest prenatal ultrasound.

The other studied factors were as follows: maternal age, parity, scarred uterus, Body Mass Index (BMI) (calculated based on pre-pregnancy weight), active smoking during pregnancy, pregestational diabetes, notable maternal pathologies, previous preterm delivery, known uterine malformations, type of pregnancy (singleton or twin), type of prematurity (spontaneous or induced), type of anesthesia, uterine injury during extraction, any difficulty during fetal extraction, and a five-minute Apgar score. Indications of caesarean delivery were also collected depending on the principal identified cause reported in the medical files and divided into six mutually exclusive groups, as previously published in cohort EPIPAGE 2:²⁴ preterm labor without preterm premature rupture of membranes, preterm premature rupture of membranes, hypertensive disorders without suspected fetal growth restriction, hypertensive disorders with suspected fetal growth restriction, placental abruption after an uncomplicated pregnancy, and suspected fetal growth restriction without hypertensive disorders. Suspected

fetal growth restriction was defined by an estimated fetal weight in less than the 5th centile on customized birth weight curves.²⁵

The Data Protection Authority (*General Data Protection Regulation / AP-HM no. 2018-89*) approved this study. According to French regulations, this study is exempt from institutional board review, because it is an observational and retrospective investigation using anonymized data from medical records. The mothers were informed that their records would be used for the evaluation of medical practices and that they could opt out of these studies.

Statistical analysis

We first described the principal characteristics of our study population. Categorical variables were presented as effectives, percentages, and continuous variables, were shown as mean \pm standard deviation (SD).

We then performed a univariate analysis to compare maternal, obstetrical, and neonatal characteristics depending on the occurrence of SMM. Categorical variables were compared with a χ^2 test or Fisher exact test when appropriate. For the continuous variables, the data were analyzed using *t* tests or a Mann-Whitney test when appropriate.

We performed a multivariate logistic regression model to quantify the association between gestational age and SMM with an adjusted odds ratio (aOR) and a 95% confidence interval (95% CI). The variables included in the multivariate model were (i) gestational age (main factor studied); (ii) notable maternal pathologies and type of prematurity (forced variables due to known prognostic interest in the literature); and (iii) variables with *p* values < 0.20 in the univariate analysis (candidate variable). A stepwise backward regression was applied in order to keep only statistically significant variables and forced adjusting variables in the final model. Firth correction was applied to take into account the small number of events.²⁶ There were no missing data concerning the main studied factors and the principal endpoint. Data

138 was analyzed using R studio V.1.2.1335, and the R package `logistf` was used. All tests were
139 two-sided, with statistical significance defined as $p < 0.05$.

Results

Population

Among the 5401 women who delivered at the two tertiary centers, 1400 mothers had a caesarean delivery, 797 (56.9%) in Conception hospital and 603 (43.1%) in North hospital between January and December 2018, and 262 (18.7%) women had a caesarean delivery between 22 and 34 weeks. More precisely, 262 women had a cesarean delivery between 24 and 34 weeks since no cesarean delivery was performed before 24 weeks during the study period. After the application of the exclusion criteria, 252 women were included in the study (Figure 1).

The maternal, obstetrical, and neonatal characteristics of the study population are described in Table 1. We couldn't present the results of umbilical arterial pH since we had missing data.

Among the 34 (13.5%) mothers presenting notable maternal pathology, eight with chronic hypertension, three with cardiac pathology (e.g., dilated cardiomyopathy with cardiac transplantation, restrictive cardiomyopathy, or rhythm troubles), three with nephropathy, two with infectious chronic diseases (e.g., VIH, VHC), three with thrombophilia, two with hemoglobin S disease, four with neurologic pathology (e.g., multiple sclerosis, epilepsy, or brachycephalic trunk hypoplasia), two with antiphospholipid syndrome or lupus, one with hematologic pathology (e.g., Willebrand), one with Crohn's disease, two with pulmonary pathology (e.g., cystic fibrosis with pulmonary transplantation), and two with venous thromboembolism were identified.

SMM occurred in 89 (35.3%) of the cases: 30 (12%) mothers had postpartum hemorrhage, 19 (7.5%) needed blood transfusions, three (1.2%) had injuries to adjacent organs (urological or vascular), five (2%) had unplanned procedures/return to theatre (because of abscess or hematoma of abdominal wall), 11 (4.4%) were admitted to the ICU, 15 (6%) presented

postpartum fever, and one mother died. The death of this mother occurred during caesarean delivery performed for severe preeclampsia and was due to pulmonary embolism. The cesarean delivery was performed in 67 (26.6%) cases in the context of spontaneous prematurity. In these cases, the indications of the cesarean delivery were mostly: breech presentation in 41 (61.2%), non-reassuring fetal hearth rate in 7 (10.4%) and suspected intra-uterine infection in 7 (10.4%).

Univariate analysis

The following factors were positively associated with SMM: gestational age (29.2 ± 2.6 weeks vs 30.1 ± 2.5 weeks; $p=0.01$), known uterine malformations (3(3.4%) vs 0; $p=0.03$), general anesthesia (21 (23.6%) vs 18 (11.0%); $p=0.01$), and uterine injury during extraction (6 (6.7%) vs 2 (1.2%); $p=0.02$). Twin pregnancy was negatively associated with SMM (11 (12.4%) vs 37 (22.7%); $p=0.04$) (Table 2).

Multivariate analysis

After multivariate analysis, gestational age was independently associated with SMM (adjusted Odds Ratio [aOR] 0.87; 95% Confidence Interval [CI] 0.78-0.97; $p=0.01$) (Table 3). The other variables statistically associated with SMM were type of pregnancy with a negative association with twin pregnancy (aOR, 0.44; 95% CI, 0.20-0.93; $p=0.03$) and with general anesthesia (aOR, 2.52; 95% CI, 1.25-5.13; $p=0.01$). The other variables included in the multivariate analysis (e.g., notable maternal pathology and type of prematurity) were not independently associated with SMM.

Two sensitivity analyses were then performed with the same variables and with a gestational age according to two modalities (< 26 weeks and ≥ 26 weeks; < 28 weeks and ≥ 28 weeks). This analysis failed to find a significant association between gestational age < 26 weeks and SMM (aOR, 2.01; 95% CI, 0.77-5.31, $p=0.15$). It did, however, find an association (at the

189 limit of significance) between gestational age < 28 weeks and SMM (aOR, 1.80; 95% CI,
190 0.99-3.27, $p = 0.05$).

Discussion

Our study showed that gestational age was independently and negatively associated with SMM in the case of preterm caesarean delivery between 22 and 34 weeks. More precisely, gestational age between 24 and 34 weeks was negatively associated with SMM since no caesarean delivery was performed before 24 weeks.

These results confirm our findings from a national population-based cohort study, EPIPAGE 2.¹⁹ Whereas previous articles reported a higher rate of SMM for caesarean delivery than vaginal delivery regardless of gestational age^{14,27–29} or an association between prematurity and maternal morbidity regardless of the mode of delivery,^{21,30} our study confirmed the association between gestational age and SMM in the case of preterm caesarean delivery.

Twin pregnancy, which has a high incidence within the population of preterm deliveries (19% in our study), was independently and negatively associated with SMM for preterm caesarean delivery. This result is consistent with the hypothesis that the SMM of extremely preterm caesarean delivery is related to the incision of a deepen myometrium. In fact, in the case of extremely preterm singleton delivery, the lower uterine segment is usually not yet formed. In contrast, in the case of extremely preterm twin delivery, the lower uterine segment forms earlier, and the incision takes place in a thinner myometrium. This is consistent with previous published results about the increased risk of intraoperative adverse events in the case of singleton pregnancy.¹⁸

We did not find an independent association between SMM and notable maternal pathology, even if highly heterogeneous, or between SMM and the type of prematurity (spontaneous or induced). This is an additional concept to consider that the SMM of preterm caesarean delivery is related to the surgical act itself. General anesthesia was significantly associated with SMM. This could be explained because of the maternal indication of general anesthesia in most cases (HELLP syndrome for example).

We reported SMM in 89 (35.3%) of the cases in our cohort, which is substantial. This finding should be included in shared decision-making process between parents, neonatologists, and obstetricians, particularly if vaginal delivery could be considered as an option (e.g., spontaneous preterm labor without abnormal fetal heart rate). In accordance with a patient-centered approach,³¹ shared decision-making aims to enable patients “to take an active role in deciding about and planning their health care”. The shared decision-making process, and particularly the agreement between obstetricians and neonatologists, is essential, as previously reported by Guinsburg et al..⁹ In fact, disagreement in the proactive management of extreme prematurity has been associated with an increased risk of death of 2.39 times in the first day of the neonates.⁹ In ten European regions between 2003 and 2012, the lowest gestational age at which maternity units reported performing a caesarean delivery for the acute distress of a singleton non-malformed fetus significantly decreased when parents were in favor of active management (from an average of 24.7 weeks in 2003 to 24.1 weeks in 2012) and when parents were against of active management (from an average of 26.1 weeks in 2003 to 25.2 weeks in 2012).³² The shared decision-making process should take into account these practice evolutions, the wishes of parents, and available data.³³ As recently suggested by Sandall et al., the key message of the information delivered to the parents could be “a caesarean section is a life-saving intervention for specific complications during pregnancy and childbirth that should be available for all women in need” and “a caesarean section also confers an increased risk of maternal morbidity, severe acute morbidity, and adverse outcomes in subsequent pregnancies when compared with vaginal delivery”.³⁴

The strength of our study was its evaluation of SMM. Despite the retrospective design of the study, the prospective filling of each electronic medical file allowed us to obtain reliable data and define a composite outcome with consistent variables. In the literature, the definition of SMM is not standardized, but we chose to generate a “synthesis” of each identified definition.

In fact, SMM is sometimes defined as a blood transfusion and/or hysterectomy to define severe postpartum hemorrhage, ICU admission, death, and length of hospitalization exceeding seven days.³⁵ Other studies have defined SMM as the occurrence of an infection, surgical injury, endometritis, readmission, or reopening or an unexpected procedure.^{21,23} The threshold of 500 mL and not 1000 mL was chosen to define postpartum hemorrhage in our cohort of cesarean deliveries and could be discussed. We chose to follow French and international definition²⁰ and think that this is not a limit since we only compared women having cesarean deliveries and not women having vaginal delivery versus cesarean delivery. We did not choose maternal hospital stays exceeding seven days in our composite outcome, because, in this case, the length of stay could be related to neonatal hospitalization.

The main limitation of our study was its small size. Although our study took place in only two centers, the recency of the collection of data (2018) optimizes the external validity of our results. Furthermore, the short duration of the inclusion period allowed us to avoid bias related to the evolution of practices over time, as it was in previous published retrospective studies.¹⁸ The aOR of the gestational age < 26 weeks is close to the aOR we reported in our previous study.¹⁹ Due to a lack of power, we failed to find a significant association between gestational age < 26 weeks and SMM in the present analysis.

Our study suggests that lower gestational age is related to a greater risk of SMM for preterm caesarean delivery between 22 and 34 weeks. These results should encourage reflection, research, and teamwork between neonatologists and obstetricians to improve agreement and shared decision-making processes with parents.

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266 **Author contributions**

267 **Delphine Sirgant:** Data curation, Writing – original draft, Formal analysis, Final approval;

268 **Noémie Rességuier:** Conceptualization, Methodology, Supervision analysis, Writing –

269 review and editing, Final approval; **Claude d’Ercole:** Conception, Supervision, Revision and

270 Validation the work, Final approval; **Pascal Auquier:** Design, Methodology, Revision and

271 Validation the work, Final approval; **Barthélémy Tosello:** Interpretation of data for the work,

272 Writing – review and editing, Validation, final approval; **Julie Blanc:** Conceptualization,

273 Formal analysis, Writing – original draft, Final approval.

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375

376

377 **Figure caption list**

378 **Figure 1.** Flow chart of the study population

Tables

Table 1. Maternal, obstetrical, and neonatal characteristics of the study population

Characteristics	N = 252
Maternal characteristics	
Maternal age, years	31.2 ± 6.0
Parity	1.15 ± 1.47
Preconceptional BMI, kg/m ²	25.6 ± 6.2
Active smoking	42 (16.9)
Pregestational diabetes	3 (1.2)
Notable maternal pathology ^a	34 (13.5)
Previous preterm delivery	26 (10.3)
Known uterine malformation	3 (1.2)
Scarred uterus	70 (27.8)
Characteristics of pregnancy	
Assisted Reproductive Technology	28 (11.1)
Type of pregnancy	
Singleton	204 (81.0)
Twin	48 (19.0)
Characteristics of delivery	
Gestational age, weeks	29.8 ± 2.6
Gestational age < 28 weeks	64 (25.4)
Gestational age ≥ 28 weeks	188 (74.6)
Type of prematurity	
Spontaneous	67 (26.6)
Induced	185 (73.4)

Indications of caesarean delivery	
Spontaneous preterm labour	64 (25.4)
Preterm premature rupture of membranes	48 (19.0)
Hypertensive disorders without suspected foetal growth restriction	36 (14.3)
Hypertensive disorders with fetal growth restriction group	28 (11.1)
Placental abruption after uncomplicated pregnancy	11 (4.4)
Suspected foetal growth restriction without hypertensive disorders	56 (22.2)
Other	9 (3.6)
General anaesthesia	39 (15.5)
Uterine injury during extraction	8 (3.2)
Difficulty of foetal extraction	15 (6.0)
Severe Maternal Morbidity	89 (35.3)
Classical incision	45 (18.2)
Postpartum haemorrhage	30 (12.0)
Transfusion	19 (7.5)
Any injury to adjacent organs ^b	3 (1.2)
Postpartum fever	15 (6.0)
Unplanned procedure/return to theatre	5 (2.0)
Intensive Care Unit (ICU) stay longer than 24 hours	11 (4.4)
Death	1 (0.4)
Neonatal characteristics	
Antenatal corticosteroids	199 (79.3)
Magnesium sulfate	169 (67.9)
Birth weight, g	1228.7 ± 500.7
5-min Apgar score	7.8 ± 2.1

379 BMI, Body Mass Index
380 weeks, weeks of gestation
381 ICU, Intensive Care Unit
382 ^aChronic hypertension, cardiac pathology, nephropathy, infectious chronic disease,
383 thrombophilia, hemoglobine S disease, neurologic pathology, antiphospholipid syndrome,
384 lupus, hematologic pathology, Crohn's disease, pulmonary pathology, or venous
385 thromboembolism
386 ^burological (1) or vascular (2)
387 Data is n (%) or mean \pm standard deviation

Table 2. Association between maternal and neonatal characteristics and Severe Maternal Morbidity: Univariate Analysis

Characteristics	SMM group n= 89	Whitout SMM group n=163	P
Maternal characteristics			
Maternal age, years	31.7 ± 6.4	30.9 ± 5.8	0.35
Parity	1.3 ± 1.7	1.1 ± 1.3	0.42
Preconceptional BMI, kg/m2	26.0 ± 6.6	25.3 ± 6.0	0.39
Active smoking	14 (15.9)	28 (17.4)	0.79
Pregestational diabetes	2 (2.3)	1 (0.6)	0.27
Notable maternal pathology ^a	12 (13.5)	22 (13.5)	0.97
Previous preterm delivery	9 (10.1)	17 (10.4)	0.98
Known uterine malformation	3 (3.4)	0	0.03
Scarred uterus	24 (27.0)	46 (28.2)	0.85
Characteristics of pregnancy			
Assisted Reproductive Technology	9 (10.1)	19 (11.7)	0.75
Type of pregnancy			0.04
Singleton	78 (87.6)	126 (77.3)	
Twin	11 (12.4)	37 (22.7)	
Characteristics of delivery			
Gestational age, weeks	29.2 ± 2.6	30.1 ± 2.5	0.01
Gestational age < 28 weeks	29 (32.6)	35 (21.5)	0.05
Gestational age ≥ 28 weeks	60 (67.4)	128 (78.5)	
Type of prematurity			0.90

Spontaneous	24 (27.0)	43 (26.4)	
Induced	65 (73.0)	120 (73.6)	
General anaesthesia	21 (23.6)	18 (11.0)	0.01
Uterine injury during extraction	6 (6.7)	2 (1.2)	0.02
Difficulty during foetal extraction	8 (9.0)	7 (4.4)	0.14
Neonatal characteristics			
Birth weight, g	1177.1 ± 532.3	1256.9 ± 481.9	0.23
5 min Apgar score <7	27 (31.4)	29 (18.0)	0.02

388 BMI, Body Mass Index

389 SMM, Severe Maternal Morbidity

390 ^aChronic hypertension, Cardiac pathology, nephropathy, infectious chronic disease,
391 thrombophilia, hemoglobine S disease, neurologic pathology, antiphospholipid syndrome,
392 lupus, hematologic pathology, Crohn's disease, pulmonary pathology, or venous
393 thromboembolism

394 Data are n (%) or mean ± standard deviations

395 Boldface type indicates significance ($p < 0.05$)

Table 3. Association between Severe Maternal Morbidity (SMM) and maternal characteristics: multivariate analysis

Variables	Adjusted OR (CI 95%)
Gestational age, weeks	0.87 (0.78-0.97)
Notable maternal pathology ^a	1.13 (0.50-2.46)
Type of pregnancy	
Singleton	1
Twin	0.44 (0.20-0.93)
Type of prematurity	
Induced	1
Spontaneous	1.15 (0.60-2.17)
General anaesthesia	2.52 (1.25-5.13)

OR, Odds Ratio (adjusted for gestational age, notable maternal pathology, type of pregnancy, type of prematurity and general anaesthesia)

CI, Confidence Interval

weeks, weeks of gestation

^aChronic hypertension, Cardiac pathology, nephropathy, infectious chronic disease, thrombophilia, hemoglobine S disease, neurologic pathology, antiphospholipid syndrome, lupus, hematologic pathology, Crohn's disease, pulmonary pathology, or venous thromboembolism

Boldface type indicates significance ($p < 0.05$)

Table 3 bis. Association between Severe Maternal Morbidity (SMM) and maternal characteristics: multivariate analysis

Variables	Adjusted OR (CI 95%)
Gestational age < 28 weeks	1.80 (0.99-3.27)
Notable maternal pathology ^a	1.00 (0.45-2.13)
Type of pregnancy	
Singleton	1
Twin	0.44 (0.20-0.91)
Type of prematurity	
Induced	1
Spontaneous	1.20 (0.64-2.25)
General anaesthesia	2.58 (1.29-5.24)

OR, Odds Ratio (adjusted for gestational age, notable maternal pathology, type of pregnancy, type of prematurity and general anaesthesia)

CI, Confidence Interval

weeks, weeks of gestation

^a Chronic hypertension, Cardiac pathology, nephropathy, infectious chronic disease, thrombophilia, hemoglobine S disease, neurologic pathology, antiphospholipid syndrome, lupus, hematologic pathology, Crohn's disease, pulmonary pathology, or venous thromboembolism

Boldface type indicates significance ($p < 0.05$)

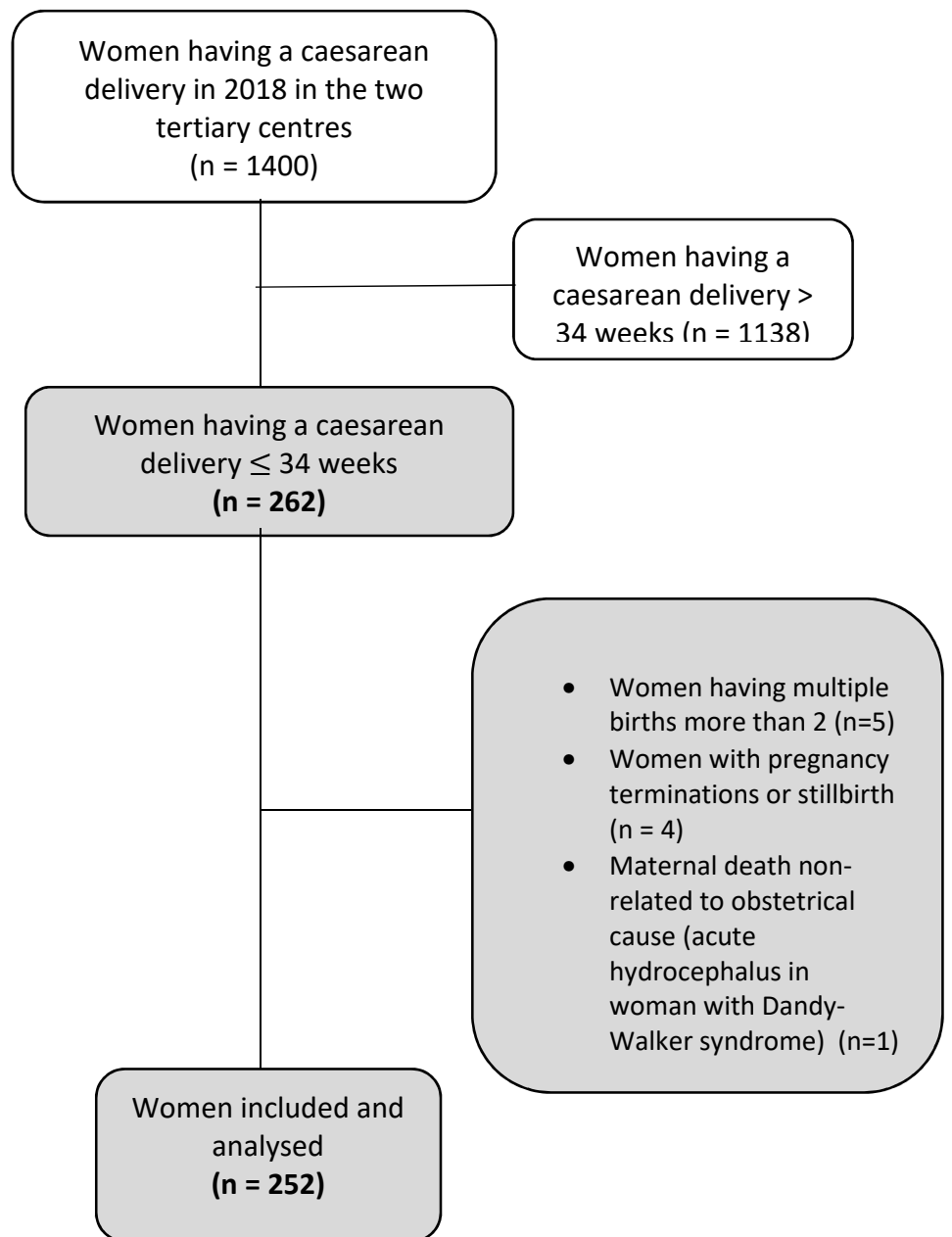


Figure 1 Flow chart of the study population