

# Severe maternal morbidity and risk of cardiovascular disease: Recent advances

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## ABSTRACT

Pregnancy complications including severe maternal morbidity have been linked with an increased risk of cardiovascular disease, and provide opportunities to identify women who would benefit from prevention. Severe maternal morbidity comprises life-endangering complications around the time of pregnancy and delivery. Literature on the relationship between severe maternal morbidity and cardiovascular disease is increasing at a rapid pace. Studies have shown that severe preeclampsia or eclampsia and severe hemorrhage are associated with cardiovascular disease later in life. Proposed pathways include endothelial damage, hypercoagulability, and impaired cardiac function that are induced or exacerbated by severe pregnancy complications that elevate cardiovascular risks. However, less is known about other types of severe maternal morbidity that may influence the risk of cardiovascular disease. Other research gaps include a need to better understand the pathways and mechanisms linking severe maternal morbidity with cardiovascular disease, the potential for cardiovascular recovery after severe cardiovascular events during pregnancy, and disparities in the occurrence of cardiovascular disease after severe maternal morbidity.

**Key words:** cardiovascular disease, heart disease, maternal near-miss, pregnancy complications, severe maternal morbidity

## INTRODUCTION

Adverse pregnancy outcomes, including severe maternal morbidity, are receiving increasing attention for their potential link with cardiovascular disease [1, 2]. Pregnancy complications such as preeclampsia, gestational diabetes, and stillbirth have been associated with more than 1.5 times greater risk of cardiovascular disease in several studies [1–4]. There is a growing push for research to identify pregnancy-specific characteristics that may be targeted to improve cardiovascular outcomes, particularly since women are more likely to have advanced sequelae than men or die after myocardial infarction and other acute cardiovascular incidents [5, 6]. Pregnancy provides opportunities to detect women at risk of adverse cardiovascular outcomes and deliver tailored interventions to prevent disease.

Severe maternal morbidity is the most recent pregnancy complication that has garnered notice from obstetrical and cardiovascular epidemiologists [7]. Severe maternal morbidity includes events such as eclampsia, amniotic fluid embolism, and obstetric shock, which are considered life-threatening during pregnancy. The incidence of severe maternal morbidity appears to be increasing in several countries owing to advanced maternal age and an increasing prevalence of predisposing risk factors [8, 9]. A number of studies are beginning to document associations between severe maternal morbidity and cardiovascular disease [7, 10]. A comprehensive review of existing literature is warranted to summarize current evidence of the relationship between severe maternal morbidity and cardiovascular disease and identify potential research gaps that need to be filled.

**Table 1.** Common definitions of severe maternal morbidity

Organization	Definition of severe maternal morbidity
World Health Organization	Maternal near-miss based on clinical, laboratory, and management criteria: shock, hysterectomy, transfusion of $\geq 5$ units of red cells, intubation, and ventilation Potential life-threatening conditions: severe hemorrhage, hypertensive disorders of pregnancy, intensive care unit admission
Centers for Disease Control and Prevention, jointly with the American College of Obstetricians and Gynecologists	21 indicators: acute myocardial infarction, aneurysm, acute renal failure, adult respiratory distress syndrome, amniotic fluid embolism, cardiac arrest/ventricular fibrillation, conversion of cardiac rhythm, disseminated intravascular coagulation, eclampsia, heart failure/arrest during surgery or procedure, puerperal cerebrovascular disorders, pulmonary edema/acute heart failure, severe anesthesia complications, sepsis, shock, sickle cell disease with crisis, air and thrombotic embolism, blood product transfusion, hysterectomy, temporary tracheostomy, ventilation
Canadian Perinatal Surveillance System	13 broad types (44 subtypes): Severe preeclampsia/eclampsia, severe hemorrhage, intensive care unit admission, hysterectomy, surgical complications, sepsis, embolism/shock/disseminated intravascular coagulation, assisted ventilation, cardiac and cerebrovascular conditions, severe uterine rupture, acute renal failure, other (sickle cell anemia, hepatic failure, acute abdomen, adult respiratory distress syndrome, and similar disorders)

## DEFINITION

Severe maternal morbidity is a composite term for unexpected complications occurring around pregnancy and delivery that are serious and threaten a woman's life [11]. Up to 88% of maternal deaths are attributed to severe maternal morbidity [12]. Conditions such as stroke, acute renal failure, and myocardial infarction are all examples of severe maternal morbidities. Severe maternal morbidity is sometimes termed a maternal "near-miss", as a high proportion of women may die without early intervention [11, 13]. More than 30% of cases of severe maternal morbidity are considered preventable through early identification and treatment [14]. The World Health Organization and obstetric institutions such as the American College of Obstetricians and Gynecologists recommend ongoing surveillance of severe maternal morbidity to identify areas for improvement in maternal healthcare [11, 13, 14].

There is a lack of consensus on the definition of severe maternal morbidity between international bodies (Table 1). The World Health Organization defines a maternal near-miss as a case in which a woman survives serious acute complications around delivery [13]. The Centers for Disease Control and Prevention and Canadian Perinatal Surveillance System define severe maternal morbidity as pregnancy-related conditions associated with significant sequelae, prolonged hospitalization, and high case fatality [15, 16]. Most definitions of severe maternal morbidity include severe preeclampsia or eclampsia, stroke, hysterectomy, and intensive care unit admission [13, 15, 16]. The consensus is that severe maternal morbidity includes life-threatening conditions occurring up to 6 weeks postpartum [13, 15, 16].

## PREVALENCE

For each maternal death, it is estimated that there are 20 or more cases of severe maternal morbidity [17]. The incidence of severe maternal morbidity is approximately 1.6% in North America, 1.2% in Australia, and 0.7% in the Netherlands [16, 18–20]. Variation in incidence is partly due to differences in the definition and measurement of severe maternal morbidity.

While the number of maternal deaths has decreased in high-income countries, the incidence of severe maternal

morbidity appears to have remained stable or risen in some regions [16, 20, 21]. In the US, greater use of blood transfusion for pregnancy hemorrhage appears to account for most of the increase in severe maternal morbidity [15, 21]. On the other hand, increasing rates of severe maternal morbidity in Canada are thought to be due to a rise in the prevalence of cerebrovascular accidents, acute renal failure, and hysterectomy [16]. Some of the observed increases may be due to better measurement and surveillance of severe maternal morbidity with time. Regardless of the reason for the increase, rising trends in severe maternal morbidity have implications for pregnant women and are an economic burden for public healthcare.

## RISK FACTORS

Risk factors for severe maternal morbidity include obesity, Black race, advanced maternal age, cesarean delivery, and pre-existing comorbidities such as chronic hypertension [8, 9, 15]. The rise in severe maternal morbidity is partly attributed to increasing rates of obesity, advanced maternal age, use of artificial reproductive techniques, and cesarean delivery [15, 22, 23]. Pregnant women over 40 years of age have a 1.6 to 2.7 times higher risk of severe maternal morbidity while infertility treatment is associated with a 1.4 times higher risk [22, 23]. Other risk factors for severe maternal morbidity include mental health disorders and disability [24, 25]. As some of these risk factors continue to be prevalent, severe maternal morbidity will likely remain an important item on the research agenda in the immediate future.

## PROGNOSIS

Overall, women with severe maternal morbidity have lengthier postpartum hospital stays and approximately double the risk of hospital readmission within the first year of delivery, compared with no morbidity [12, 26–28]. Severe maternal morbidity is linked with adverse mental health, including post-traumatic stress disorder and other psychiatric illnesses within one year of birth [29–31]. Studies beyond the first year are scarce, but a few have reported that women with severe maternal morbidity have a lower perceived quality of life up to five years

**Table 2.** Summary of studies examining the risk of cardiovascular disease after severe maternal morbidity

Author, publication year	Type of severe maternal morbidity	Outcome; length of follow-up	Country; data source	Sample size	Adjusted risk estimate (95% CI)
Behrens, 2016	Severe preeclampsia	Cardiomyopathy; 34 years	Denmark; National Patient Register and Medical Birth Register (1978–2012)	2 067 633 pregnancies	HR, 2.22 (1.47–3.36) for cardiomyopathy 5 years after the latest delivery HR, 2.20 (1.50–3.23) for cardiomyopathy >5 months after the first delivery
Cartus, 2021	Any severe maternal morbidity following conditions listed by the Centers for Disease Control and Prevention	Atrial fibrillation, heart failure, ischemic heart disease (including acute myocardial infarction), stroke, transient ischemic attack, and a composite outcome of any of these events; 26 months	US; Pennsylvania Medicaid administrative claims data (2016–2018)	137 140 deliveries	RD, 27.9 (18.6–37.2)
Cho, 2021	Postpartum hemorrhage requiring transfusion	Any cardiovascular hospitalization; 8 years	Korea; Korea National Health Insurance claims, National Health Screening Examination and National Health Screening Program for Infants and Children (2007)	150 381 deliveries	HR, 1.60 (1.25–2.06)
Kestenbaum, 2003	Severe preeclampsia/ /eclampsia	Hospitalizations for acute myocardial infarction, acute stroke or coronary artery revascularization procedure, including coronary artery bypass graft; 13 years	US; Washington State Birth Events Record Database (1987–1998)	124 141 deliveries	HR, 3.3 (1.7–6.5)
Lykke, 2010	Severe preeclampsia/ /eclampsia	Death from cardiovascular causes; 30 years	Denmark; National Patient Registry (1978–2007)	782 287 deliveries	HR, 2.89 (1.93–4.33)
Ukah, 2020	Any hemorrhage requiring transfusion	Any cardiovascular hospitalization; 30 years	Canada; Maintenance and Use of Data for the Study of Hospital Clientele registry, Quebec (1989–2016)	1 224 975 deliveries	HR, 1.47 (1.23–1.76) for any hemorrhage with transfusion HR, 1.85 (1.28–2.68) for antenatal hemorrhage with transfusion HR, 1.85 (0.95–3.58) for placenta praevia with transfusion HR, 1.41 (0.58–3.43) for peripartum hemorrhage with transfusion HR, 1.38 (1.13–1.68) for postpartum hemorrhage with transfusion
Ukah, 2022	Any severe maternal morbidity following conditions listed by the Canadian Perinatal Surveillance System	Any cardiovascular hospitalization; 31 years	Canada, Maintenance and Use of Data for the Study of Hospital Clientele registry, Quebec (1989–2019)	1 224 975 deliveries	HR, 1.77 (1.72–1.82)
Wikstrom, 2005	Severe preeclampsia/ /eclampsia	Ischemic heart disease; 15 years	Sweden; Swedish Medical Birth Register (1973–1982)	403 550 deliveries	IRR, 2.8 (2.2–3.7)
Yeh, 2014	Eclampsia	Any cardiovascular hospitalization; 12 years	Taiwan; Taiwan National Health Insurance database (1997–2009)	6 300 deliveries	HR, 1.38 (0.28–6.83)

Abbreviations: CI, confidence interval; HR, hazard ratio; IRR, incidence rate ratio; RD, risk difference

after delivery and an increased risk of mortality in the long term [32–35].

Recent studies are beginning to show an association with cardiovascular disease (Table 2) [7, 10]. In an analysis of Medicaid administrative claims data from Pennsylvania in the US, it was demonstrated that severe maternal morbidity was associated with an increased risk of adverse cardiovascular outcomes in the first two years following pregnancy [10]. The investigators assessed the association with cardiovascular events such as stroke, transient ischemic attack, heart failure, and ischemic heart disease using the Centers for Disease Control and Prevention's definition of severe

maternal morbidity [15]. Among 137 140 deliveries, the cumulative incidence of severe maternal morbidity was 4.2% [10]. After accounting for ethnicity, age, parity, mode of delivery, Medicaid eligibility, substance use disorders, and a range of maternal comorbidities, severe maternal morbidity was associated with an excess of 2.7 cardiovascular events per 1000 deliveries at one month postpartum (95% CI, 1.6–3.8) and 27.9 cardiovascular events per 1000 deliveries at 26 months postpartum (95% CI, 18.6–37.2). Severe maternal morbidity was most strongly associated with heart failure, with 12.1 excess cases per 1000 deliveries at 26 months postpartum (95% CI, 6.2–18.0).

A second study used hospital data from Canada in which pregnant women had up to three decades of follow-up [7]. The investigators followed 1.3 million women who delivered in Quebec to identify subsequent cardiovascular admissions over time [7]. Severe maternal morbidity occurred in 5% of women in the cohort and included conditions specified by the Canadian Perinatal Surveillance System [16]. A range of cardiovascular outcomes was examined including heart disease, cerebrovascular disease, pulmonary vascular disease, and cardiovascular interventions in the thirty years following delivery. Compared with no morbidity, severe maternal morbidity was associated with 1.8 times higher risk of any cardiovascular disease (95% CI, 1.72–1.82) and more than double risk of heart failure, cardiomyopathy, and pulmonary vascular conditions. Results were adjusted for confounders including maternal age at delivery, socioeconomic deprivation, comorbidity, substance use disorders, multiple gestation, and time.

In addition to examining severe maternal morbidity as a composite exposure, the investigators assessed the association of individual types of severe maternal morbidity with the risk of cardiovascular disease. Most types of severe maternal morbidity were associated with an elevated risk of cardiovascular disease, but serious cardiac complications during pregnancy were associated with the greatest risk (hazard ratio 5.37; 95% CI, 4.65–6.20). Assisted ventilation, cerebrovascular accidents, and admission to the intensive care unit were associated with more than triple the risk of cardiovascular disease. Furthermore, the investigators were able to demonstrate that associations differed depending on the length of time after delivery [7]. Severe maternal morbidity was associated with cardiovascular disease throughout follow-up, but the risks were greatest in the immediate period after delivery and declined slowly with time.

### **PATHWAYS TO CARDIOVASCULAR DISEASE**

These novel findings have led to speculation about the pathways linking severe maternal morbidity with cardiovascular disease. Pathways may vary. Patients with severe maternal morbidity may have an underlying predisposition to cardiovascular disease [36]. Conditions such as severe preeclampsia, severe hemorrhage, and peripartum cardiomyopathy share common risk factors with cardiovascular disease, including smoking, obesity, hypertension, and Black race [36–38]. Similarly, preeclampsia is associated with an increased risk of renal disease, an additional risk factor for cardiovascular disease [37, 39]. Proposed mechanisms include insufficient spiral artery remodeling, oxidative stress, endothelial cell dysfunction, and exaggerated inflammatory responses in conditions such as preeclampsia, acute renal failure, and sickle cell crises [7, 36, 37, 40, 41].

There is ample literature on the risk of cardiovascular disease following preeclampsia, with most of this work summarized in literature reviews [42, 43]. However, only a few studies have investigated severe preeclampsia or eclampsia as components of severe maternal morbidity (Table 2) [7, 44–48]. The studies had sample sizes ranging from 6300 to over 2 million pregnancies from Denmark [45, 47], Sweden [48], the US [44], and Taiwan [46]. Severe preeclampsia and eclampsia were found to be associated with a 1.4 to 3.3-fold increase in the risk of cardiovascular disease and mortality, compared with uncomplicated pregnancies. In one systematic review [1], the pooled odds ratio was 2.74 (95% CI, 2.48–3.04) for the association of severe preeclampsia with cardiovascular disease. In patients with preeclampsia, an imbalance in levels of placental growth factor and sFlt-1 may result in endothelial or vascular damage [36, 37]. Severe maternal morbidity, including severe preeclampsia, is often marked by hypercoagulability and elevated C-reactive protein levels that may exacerbate an inflammatory response [37]. Both hypercoagulability and excessive inflammatory reactions have been linked with cardiovascular disease [36, 37].

Severe maternal morbidity including hemorrhage may harm the cardiovascular system directly [36]. Severe hemorrhage can lead to hemorrhagic shock that impairs cardiac function [49, 50]. Excessive loss of blood has been linked with hemodynamic instability and end-organ damage [50]. Transfusion of blood, even in the absence of hemorrhage, is associated with venous thromboembolism, which may confer further cardiovascular risks [50, 51]. Some patients may not completely recover cardiac function in the postpartum period, leading to the development of long-term cardiovascular pathology [7, 52]. A growing number of studies have examined hemorrhage-related conditions during pregnancy and the risk of cardiovascular disease [45, 53–55]. Three studies have shown that severe postpartum hemorrhage requiring blood transfusion was associated with 1.4 to 1.6 times higher risk of subsequent cardiovascular disease, compared with no hemorrhage [7, 49, 50]. Antenatal hemorrhage requiring blood transfusion was associated with 1.9 times higher risk of cardiovascular disease in one analysis [50]. In another study, severe antepartum, intrapartum, and postpartum hemorrhage were associated with 1.5 times higher risk of developing cardiovascular disease [7].

Patients may also have undiagnosed cardiovascular disease at the time of pregnancy [36]. In patients with already existing cardiovascular conditions, the normal physiological changes of pregnancy, including increased cardiac output, elevated heart rate, and decreased vascular resistance [56], may overburden the cardiovascular system. In such situations, preexisting cardiovascular conditions may worsen and appear for the first time as a complication of pregnancy, including severe cardiac morbidity that exacerbates subsequent cardiovascular risks.

## FUTURE RESEARCH FOCUS

Despite growing awareness that women with pregnancy complications may be at risk of cardiovascular disease, literature on severe maternal morbidity remains sparse. The scarcity of studies on how specific types of severe maternal morbidity are associated with cardiovascular disease remains a key knowledge gap. Studies so far have mostly reported on severe maternal morbidity as a composite exposure or focused only on severe preeclampsia and hemorrhage. Examining additional types of severe maternal morbidity may help identify patients more at risk of cardiovascular disease. There is also a need for a uniform definition of severe maternal morbidity. Concordance on the definition of severe maternal morbidity is necessary to replicate studies in different settings and enable comparisons between regions.

Mechanisms by which severe maternal morbidity affects the cardiovascular system also need further study. The extent to which pregnant women recover after cardiovascular incidents requires attention, including women with preexisting heart disease. None of the published studies reviewed were conducted in low and middle-income countries or populations most vulnerable to severe maternal morbidity, including women of African ethnicity or with disabilities. Greater effort is needed to assess cardiovascular risks associated with severe maternal morbidity in high-risk groups.

## CONCLUSION

Current literature, although scarce, suggests that women with severe maternal morbidity have an elevated risk of cardiovascular disease. However, more research is needed in this area to identify the pathways linking severe maternal morbidity with cardiovascular disease and the types of severe maternal morbidity associated with a greater risk. Improved surveillance of women with severe maternal morbidity offers opportunities to identify, prevent, and treat future cardiovascular diseases in coming years.

## Article information

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