Original Research

Association of Epilepsy and Severe Maternal Morbidity

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OBJECTIVE: To evaluate severe maternal morbidity (SMM) among patients with epilepsy and patients without epilepsy.

METHODS: We retrospectively examined SMM using linked birth certificate and maternal hospital discharge records in California between 2007 and 2012. Epilepsy present at delivery admission was the exposure and was subtyped into generalized, focal and other less specified, or unspecified. The outcomes were SMM and nontransfusion SMM from delivery up to 42 days' postpartum, identified using Centers for Disease Control and Prevention indicators. Multivariable logistic regression models were used to adjust for confounders, which were selected a priori. We also estimated the association between epilepsy and SMM independent of comorbidities by using a validated obstetric comorbidity score. Severe maternal morbidity indicators were then compared using the same multivariable logistic regression models.

RESULTS: Of 2,668,442 births, 8,145 (0.3%) were to patients with epilepsy; 637 (7.8%) had generalized, 6,250 (76.7%) had focal or other less specified, and 1,258 (15.4%) had unspecified subtypes. Compared with patients without epilepsy, patients with epilepsy had greater odds of SMM (4.3% vs 1.4%, adjusted odds ratio [aOR] 2.91, 95% CI 2.61–3.24) and nontransfusion SMM (2.9% vs 0.7%, aOR 4.16, 95% CI 3.65–4.75). Epilepsy remained significantly associated with increased SMM and nontransfusion SMM after additional adjustment for the obstetric comorbidity score, though the effects were attenuated. When grouped by organ system, all SMM indicators were significantly more common among patients with epilepsy—most notably those related to hemorrhage and transfusion.

CONCLUSION: Severe maternal morbidity was significantly increased in patients with epilepsy, and SMM indicators across all organ systems contributed to this.

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The number of people with epilepsy in the United States is rising, increasing from 2.3 million in 2010 to 3 million in 2015.[1,2] Approximately 24,000 patients with epilepsy deliver annually, accounting for 0.3–0.5% of all births.[3,4] In these patients, the risk of maternal mortality may be as much as 11 times higher than the general population.[4–7] Seventy-nine percent of maternal deaths in a recent cohort of patients with epilepsy were considered to be sudden and unexpected, suggesting that an improved understanding of maternal mortality with epilepsy is warranted.[8]

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Although patients with epilepsy have increased maternal mortality, evidence has been conflicting regarding their risk of pregnancy complications.[3,4,9] This may be due to variability in seizure type and control, or to the rarity of specific outcomes, such as eclampsia, which have been studied. In an attempt to understand rare complications that might contribute to maternal mortality, the severe maternal morbidity (SMM) composite was developed by the Centers for Disease Control and Prevention (CDC). This composite includes 21 SMM indicator events, such as eclampsia and cardiac arrest.[10–12] As with maternal mortality, SMM has also been shown to be increased among patients with epilepsy.[4] However, it remains unclear which SMM indicator events are occurring and how SMM varies by type of epilepsy. Thus we sought to examine SMM among patients with epilepsy.

METHODS

This was a cohort study of pregnancies in California between 2007 and 2012 to assess health risks associated with maternal epilepsy in pregnancy. Data were analyzed retrospectively. Births were identified using California birth cohort files, which link data from birth certificates to maternal and neonatal discharge records through the Office of Statewide Health Planning and Development. The California birth and fetal death certificate provides information on maternal demographics, medical diagnoses, delivery complications, and infant outcomes, which are filled out by both patients and medical staff. Inpatient discharge records were obtained from all licensed acute care facilities in California, and include International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. The linkage in these birth cohort files is complete through 2012; therefore, 2012 was selected as the study endpoint.

All pregnant patients who gave birth at 20 weeks of gestation or more to a liveborn neonate or stillborn fetus were included in this study. Patients were excluded if birth certificate and maternal delivery hospitalization discharge records were not linked or if the gestational age was implausible (before 20 weeks or after 43 weeks). The Stanford University Institutional Review Board and the California State Committee for the Protection of Human Subjects reviewed and approved this study.

The exposure for this study was a maternal diagnosis of epilepsy. Only patients with an epilepsy diagnosis during an antepartum hospitalization or marked present at admission for delivery hospitalization were defined as having epilepsy. Epilepsy was further categorized into generalized epilepsy, focal or other less specified epilepsy, and unspecified subtypes based on ICD-9-CM codes. Generalized epilepsy was identified using ICD-9-CM codes 345.0 and 345.1. Focal or other less specified epilepsy included a composite of focal (345.4, 345.5), localization-related (345.7), and other types (345.2 "petit mal status," 345.3 "grand mal status," 345.8 "other forms of epilepsy and recurrent seizures," 345.9 "epilepsy unspecified"). These types were grouped owing to anticipated small numbers limiting our ability to report rare outcomes between them. Two distinct unspecified epilepsy groups were created based on frequently encountered ICD-9-CM codes; code 649.4 was used for unspecified "Epilepsy complicating pregnancy, childbirth, or the puerperium" and code 780.39 was used for "Convulsions." If patients had 780.39 and a code for eclampsia, they were excluded from the analysis because it was unclear whether this code represented the presence of epilepsy or eclampsia at admission and could result in misclassification of the exposure. If patients had codes for multiple subtypes of seizures, only the most severe specified subtype was counted. This was done in a mutually exclusive fashion in the following hierarchy: generalized; focal or other less specified; epilepsy complicating pregnancy, childbirth, or the puerperium; then lastly convulsions. For example, a patient with ICD-9-CM codes for both generalized epilepsy (eg, 345.0) and convulsions (780.39) was categorized under the generalized subtype only.

The primary outcome was the SMM composite during the delivery admission or during a subsequent hospital admission up to 42 days' postpartum. The SMM composite was defined using the CDC indicators and their corresponding ICD-9-CM codes.[12] To further understand this outcome, we reported "nontransfusion severe maternal morbidity," which is a composite of the same SMM indicators excluding blood transfusion. Blood transfusion is the only indicator for SMM in up to half of cases, and the amount of blood transfused is not recorded in administrative data.[10,13] Therefore, nontransfusion SMM was included as a co-primary outcome.

Next, all 21 SMM indicators were individually evaluated and compared between people with epilepsy and people without epilepsy. Owing to small sample size for some specific indicator events, the following organ system groups were made: cardiac (acute myocardial infarction, aneurysm, cardiac arrest or ventricular fibrillation, conversion of cardiac rhythm, heart failure or arrest during surgery, or acute heart failure), pulmonary (adult respiratory

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distress syndrome, pulmonary edema, temporary tracheostomy, or mechanical ventilation), renal (acute renal failure), hemorrhage (disseminated intravascular coagulation, shock, or hysterectomy), sepsis, obstetric (amniotic fluid embolism, eclampsia, severe anesthesia complications, or air and thrombotic embolism), other medical (puerperal cerebrovascular disorders or sickle cell disease with crisis), and transfusion (blood transfusion). Transfusion SMM was considered as a separate group from hemorrhage because of the aforementioned ambiguity in administrative data of number of units transfused and the emerging importance of nontransfusion SMM. Of note, the cerebrovascular disorder SMM indicator includes events such as subarachnoid hemorrhage, stroke, and venous sinus thrombosis.

Secondary outcomes included obstetric complications such as preeclampsia (with and without severe features), gestational diabetes, stillbirth, preterm birth, induction of labor, and cesarean birth.

Potential confounders were selected a priori based on prior literature on SMM and epilepsy and causal diagrams.[4,13,14] These included maternal age, race or ethnicity as a social determinant, method of payment, education level, trimester of prenatal care initiation, and parity (which were included as covariates in multivariable logistic regression model 2, see below). Race–ethnicity was obtained from the birth certificate, where it is self-reported by the patient. This approach has been previously validated using California birth certificate data.[15] Race–ethnicity was included as a social construct given prior literature showing associations with both epilepsy and SMM.[4,13] We additionally identified comorbidities, such as chronic cardiovascular disease, as potential confounders or mediators of the association between epilepsy and SMM. Given this, we planned a separate multivariable logistic regression model to also account for the role comorbidities might be playing in SMM for patients with epilepsy. To do so, comorbidities were added as a covariate to the aforementioned model 2 to create model 3. Comorbidities were defined using a previously developed expanded obstetric comorbidity scoring system to create a comorbidity composite.[13] This obstetric comorbidity scoring system includes 27 patient-level risk factors for SMM, such as preexisting diabetes, chronic hypertension, pulmonary hypertension, bleeding disorders, major mental health disorders, and autoimmune disease. Because the purpose of this comorbidity composite was to identify patient-level mediators or confounders preceding delivery or the outcome, preterm birth was excluded from the composite, which is in line with other validated comorbidity scores that have been published.[16,17] In addition, neuromuscular disorders were excluded from the composite given overlap with epilepsy.

Demographic and obstetric characteristics, such as mode of delivery, preterm birth, preeclampsia, and gestational diabetes, were compared with χ^2 tests for categorical variables and t tests for continuous variables. Variables that were not normally distributed were categorized based on clinically relevant cutoffs (eg, body mass index [BMI, calculated as weight in kilograms divided by height in meters squared] and maternal age), or frequency (eg, obstetric comorbidity score). Next, crude logistic regression models (model 1) were used to estimate odds ratios (ORs) with 95% CIs for the associations between epilepsy and SMM and nontransfusion SMM, using births to patients without epilepsy as the referent group. Owing to the rarity of SMM and nontransfusion SMM, ORs approximated risk ratios.

A series of additional analyses were then conducted to minimize potential bias. First, multivariable logistic regression models (model 2) were adjusted for the confounding variables listed above (maternal age, race–ethnicity as a social determinant, method of payment, education level, trimester of prenatal care initiation, and parity). Secondly, the obstetric comorbidity score described above was added as a covariate to model 2 to generate model 3. These models were run separately in the event that comorbidities served as mediators rather than confounders of the association between epilepsy and SMM. Next, multivariable logistic regression models were used to compare the odds of each of the 21 CDC SMM indicators between pregnancies with maternal epilepsy and pregnancies without maternal epilepsy, adjusted for the same potential confounders listed above in model 2. Lastly, as an assessment of the robustness of our results and analytical decisions, propensity-score matching was done to analyze the association between epilepsy and SMM and nontransfusion SMM. We used greedy nearest neighbor matching with "method nearest" in the MatchIt package in R, which matches patients with epilepsy and patients without epilepsy based on the closest propensity score to optimally balance covariates between groups. In this analysis, a distance is computed between each treated unit and each control unit, and, one by one, each treated unit is assigned a control unit as a match. The matching is "greedy" in the sense that there is no action taken to optimize an overall criterion; each match is selected without considering the other matches that may occur subsequently.[18]

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We re-ran models 2 and 3, using propensity score matching for both SMM and nontransfusion SMM and using the same covariates noted above. Significance was set to a two-tailed alpha=0.05. All statistical analysis was performed using SAS 9.4 and R 3.6.1.

RESULTS

Among 2,668,442 eligible births, 8,145 (0.3%) were to patients with epilepsy (Fig. 1). Of these, 637 (7.8%) had generalized epilepsy; 6,250 (76.7%) had focal or other less specified epilepsy; 284 (3.5%) had epilepsy complicating pregnancy, childbirth, or the puerperium; and 974 (12.0%) had convulsions.

Patients with epilepsy were more likely to be younger, Hispanic, have high BMI at delivery, have not completed college, and have commercial insurance than patients without epilepsy. Prepregnancy diabetes, chronic hypertension, and major depressive disorder were also more prevalent among patients with epilepsy, as was a higher obstetric comorbidity index score (Table 1).

Compared with patients without epilepsy, patients with maternal epilepsy were more likely to be nulliparous and develop preeclampsia without severe features or gestational hypertension and severe preeclampsia and to deliver preterm. The rate of cesarean birth with maternal epilepsy was significantly higher than without epilepsy (Table 2).

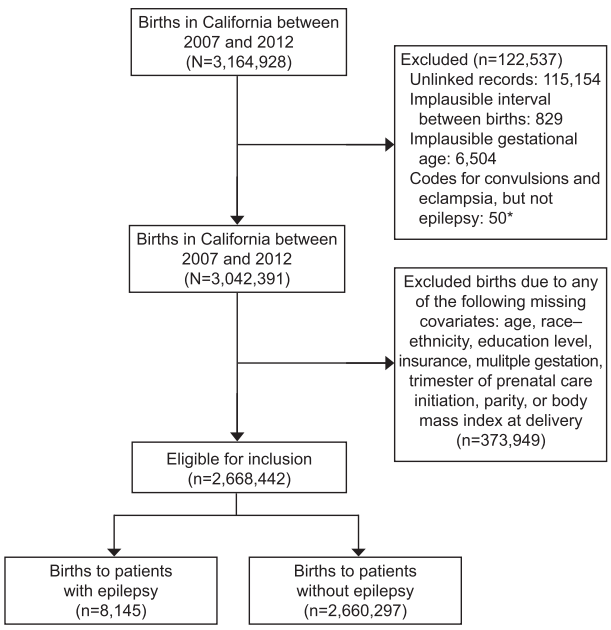

Fig. 1. Study cohort inclusion flowsheet. *Unable to distinguish exposure.

Panelli. Severe Maternal Morbidity With Epilepsy. Obstet Gynecol 2021.

Severe maternal morbidity occurred in 1.4% of all births; nontransfusion SMM occurred in 0.7% of all births. The risk of SMM was significantly increased in births with maternal epilepsy, compared with births without maternal epilepsy (4.3% vs 1.4%, crude OR 3.10 [95% CI 2.79–3.45], adjusted odds ratio [aOR] 2.91 [95% CI 2.61–3.24], Table 3) as was nontransfusion SMM (2.9% vs 0.7%, crude OR 4.52 [95% CI 3.97–5.15], aOR 4.16 [95% CI 3.65–4.75], Table 4). Generalized epilepsy was associated with the highest risk of both SMM and nontransfusion SMM. Focal or other less specified epilepsy subtypes also were associated with significantly increased risk of both SMM and nontransfusion SMM. When examining individual codes for unspecified epilepsy, SMM remained similarly increased for unspecified epilepsy complicating pregnancy, childbirth, or the puerperium, as well as for convulsions (Tables 3 and 4).

After accounting for comorbidities in model 3, the associations between any type of epilepsy and both SMM and nontransfusion SMM were attenuated but remained significant (Tables 3 and 4).

Appendix 1, available online at http://links.lww.com/AOG/C442, demonstrates the risk of each SMM indicator compared between births with and without maternal epilepsy. When grouped by organ system, all SMM indicators were significantly more common among patients with epilepsy (Fig. 2). For simplification in Figure 2, cardiac and pulmonary categories were combined but are shown separately in Appendix 1 (http://links.lww.com/AOG/C442). Compared with patients without epilepsy, the most common events among patients with epilepsy were transfusion, eclampsia, disseminated intravascular coagulation, and puerperal cerebrovascular disorders.

Lastly, the estimated associations between epilepsy and both SMM and nontransfusion SMM were overall unchanged in sensitivity analyses that used propensity score matching to account for confounders (see Appendices 2–4, available online at http://links.lww.com/AOG/C442).

DISCUSSION

Patients with epilepsy had a threefold increased risk of SMM and a fourfold increased risk of nontransfusion SMM compared with patients without epilepsy, and these risks persisted despite adjustment for maternal comorbidities. Although generalized epilepsy was rare, it was associated with the highest risk. To put our results into context, the risk of SMM with epilepsy was higher than what has been demonstrated with other conditions, such as autoimmune disease (adjusted risk ratio 1.80, 95% CI 1.73–1.87).[13] Overall, our findings

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Table 1. Demographic Characteristics of Patients With Epilepsy Compared With Patients Without Epilepsy in California, 2007–2012 (N=2,668,442)

Maternal Characteristic	Births to Patients Without Epilepsy (n=2,660,297)	Births to Patients With Epilepsy (n=8,145)	P*
Age at delivery (y)			<.001
Younger than 20	161,953 (6.1)	542 (6.7)	
20–24	584,716 (22.0)	1,987 (24.4)	
25–29	733,199 (27.6)	2,374 (29.2)	
30–34	691,045 (26.0)	1,956 (24.0)	
35–39	388,960 (14.6)	1,023 (12.6)	
40 or older	100,424 (3.8)	263 (3.2)	
Race–ethnicity			<.001
Hispanic	759,019 (28.5)	3,030 (37.2)	
Non-Hispanic White	1,370,901 (51.5)	3,554 (43.6)	
Asian or Pacific Islander	150,401 (5.7)	944 (11.6)	
Black	366,187 (13.8)	501 (6.2)	
Other†	13,789 (0.5)	116 (1.4)	
BMI at delivery (kg/m^2)			<.001
Less than 25	307,176 (11.5)	918 (11.3)	
25–29.9	989,878 (37.2)	2,799 (34.4)	
30–34.9	784,219 (29.5)	2,357 (28.9)	
35–39.9	365,089 (13.7)	1,233 (15.1)	
40 or higher	213,935 (8.0)	838 (10.3)	
Education level			<.001
High school or less	601,631 (22.6)	1,946 (23.9)	
Completed high school	711,152 (26.7)	2,541 (31.2)	
Some college	655,946 (24.7)	2,298 (28.2)	
Completed college or higher	691,568 (26.0)	1,360 (16.7)	
Delivery payment method			<.001
Medi-Cal	1,283,529 (48.3)	3,317 (40.7)	
Commercial insurance	1,291,654 (48.6)	4,664 (57.3)	
Other	85,114 (3.2)	164 (2.0)	
Trimester of prenatal care initiation			<.001
1st	2,187,846 (82.2)	6,484 (79.6)	
2nd	347,739 (13.1)	1,146 (14.1)	
3rd or None	77,781 (2.9)	306 (3.8)	
Unknown	46,931 (1.8)	209 (2.6)	
Prepregnancy diabetes (type 1 or 2)	23,771 (0.9)	175 (2.2)	<.001
Chronic hypertension	39,355 (1.5)	262 (3.2)	<.001
Major depressive disorder	3,239 (0.1)	43 (0.5)	<.001
Obstetric comorbidity score‡			
0	1,346,263 (50.6)	3,245 (39.8)	<.001
1–4	562,598 (21.2)	1,312 (16.1)	
5–9	261,895 (9.8)	849 (10.4)	
10 or higher	489,541 (18.4)	2,739 (33.6)	

Data are n (%) unless otherwise specified.
* Analyzed with χ^2 test.
† Race or ethnicity groups defined based on state reporting. Other defined as American Indian, Alaska Native, or other.
‡ Defined using a validated comorbidity scoring system that has been shown to aid in prediction of severe maternal morbidity.[13] This scoring system includes 27 patient-level risk factors for severe maternal morbidity, such as pulmonary hypertension, preexisting cardiac disease or bleeding disorders, and autoimmune disease. Owing to overlap with our exposure, we excluded neuromuscular diseases from this comorbidity score. In addition, only comorbidities present before delivery were included; therefore, preterm birth was also excluded from this comorbidity score. See text for details.

emphasize the contribution of hemorrhage to SMM for patients with epilepsy and highlight who might be at highest risk of complications.

Our results are important in light of conflicting evidence regarding the risk of pregnancy complications for patients with epilepsy.[3–6,9,19,20] Although it is reassuring that the majority of these patients (95.7%) did not experience SMM, the increased risk we identified is similar to what has been reported previously.[4] The persistent risk even after accounting for comorbidities further underscores the importance of physician awareness when managing patients with epilepsy.

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Table 2. Pregnancy Characteristics and Outcomes Among Patients With Epilepsy Compared With Those Without Epilepsy in California, 2007–2012 (N=2,668,442)

Characteristic	Births to Patients Without Epilepsy (n=2,660,297)	Births to Patients With Epilepsy (n=8,145)	P*
Nulliparous	996,833 (37.5)	3,168 (38.9)	.01
Multiple gestation	42,049 (1.6)	136 (1.7)	.52
Preeclampsia without severe features or gestational hypertension	117,674 (4.4)	487 (6.0)	<.001
Severe preeclampsia	286,662 (1.1)	177 (2.2)	<.001
Gestational diabetes	203,336 (7.6)	617 (7.6)	.82
Stillbirth	9,385 (0.4)	35 (0.4)	.24
Preterm birth (wk)	210,877 (7.9)	1,102 (13.5)	<.001
Less than 34 0/7	154,920 (5.8)	759 (9.3)	
34 0/7–36 6/7	55,957 (2.1)	343 (4.2)	
Average gestational age at delivery (wk)	38.6±2.0	38.2±2.4	<.001
Induction of labor	927,054 (34.9)	2,918 (35.8)	.06
Cesarean birth	889,026 (33.4)	3,415 (41.9)	<.001
Repeat cesarean birth	404,963 (15.2)	1,474 (18.1)	<.001
SMM	37,960 (1.4)	350 (4.3)	<.001
Nontransfusion SMM	17,309 (0.7)	234 (2.9)	<.001

SMM, severe maternal morbidity.
Data are n (%) or mean±SD unless otherwise specified.
* Categorical variables were analyzed with χ^2 test; continuous variables were analyzed with *t* test.

Seizure control is a critical component of prenatal management and is important when interpreting the risk of SMM for patients with epilepsy.[9] Seizures themselves can cause hypoxia, aspiration, or trauma from falls, which can contribute to SMM events such as pulmonary edema.[3] Although these types of events were more common for patients with epilepsy, other events such as those related to hemorrhage were also increased. Furthermore, though eclampsia contributed to SMM, it did not occur in 84.6% of patients with epilepsy who experienced SMM. Taken together, it seems that a seizure event alone–either epileptic or eclamptic–does not completely explain the increased risk of SMM with epilepsy.

To this end, research has also explored the role of antiseizure medications in augmenting the risk of adverse outcomes with epilepsy.[1,21–28] However, understanding the association between antiseizure medications and obstetric outcomes is challenging. Although greater antiseizure medication use might reflect improved seizure control and better outcomes, it can also be a proxy for disease severity and bias the signal in either direction.[14,19] Because we were unable to comment on use of antiseizure

Table 3. Adjusted Risk of Severe Maternal Morbidity Among Patients With Epilepsy Compared With Patients Without Epilepsy in California, 2007–2012 (N=2,668,442)

Exposure Group	n (Row %)	Model 1 [Crude OR (95% CI)]	Model 2* Adjusted OR (95% CI)	Model 3† Adjusted OR (95% CI)
Patients without epilepsy (n=2,660,297)	37,960 (1.4)	Ref	Ref	Ref
All patients with epilepsy (n=8,145)‡	350 (4.3)	3.10 (2.79–3.45)	2.91 (2.61–3.24)	2.13 (1.90–2.39)
Generalized epilepsy (n=637)	49 (7.7)	5.76 (4.30–7.71)	5.32 (3.97–7.14)	3.81 (2.79–5.21)
Focal epilepsy and other less specified epilepsy (n=6,250)	241 (3.9)	2.77 (2.44–3.15)	2.61 (2.29–2.97)	2.01 (1.75–2.30)
Unspecified epilepsy complicating pregnancy, childbirth, or the puerperium (n=284)	14 (4.9)	3.58 (2.09–6.13)	3.23 (1.88–5.54)	2.31 (1.30–4.11)
Convulsions only (n=974)	46 (4.7)	3.43 (2.55–4.61)	3.20 (2.38–4.31)	1.80 (1.30–2.49)

OR, odds ratio; Ref, reference.
* Model 2 adjusted for maternal age, race–ethnicity as a social determinant, method of payment, education level, trimester of prenatal care initiation, and parity.
† Model 3 additionally adjusted for validated obstetric comorbidity score. See text for details.
‡ Refer to text for details regarding categorization of epilepsy subtypes.

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Table 4. Adjusted Risk of Nontransfusion Severe Maternal Morbidity Among Patients With Epilepsy Compared With Patients Without Epilepsy in California, 2007–2012 (N=2,668,442)

Exposure Group	n (Row %)	Model 1 [Crude OR (95% CI)]	Model 2* Adjusted OR (95% CI)	Model 3† Adjusted OR (95% CI)
Patients without epilepsy (n=2,660,297)	17,309 (0.7)	Ref	Ref	Ref
All patients with epilepsy (n=8,145)‡	234 (2.9)	4.52 (3.97–5.15)	4.16 (3.65–4.75)	2.99 (2.61–3.43)
Generalized epilepsy (n=637)	38 (6.0)	9.69 (6.98–13.45)	8.83 (6.34–12.89)	6.29 (4.44–8.92)
Focal epilepsy and other less specified epilepsy (n=6,250)	162 (2.6)	4.07 (3.48–4.76)	3.78 (3.21–4.40)	2.85 (2.42–3.36)
Unspecified epilepsy complicating pregnancy, childbirth, or the puerperium (n=284)	Fewer than 15§	3.30 (1.47–7.40)	2.87 (1.28–6.47)	1.87 (0.80–4.39)
Convulsions only (n=974)	28 (2.9)	4.52 (3.10–6.58)	4.17 (2.86–6.08)	2.21 (1.47–3.33)

OR, odds ratio; Ref, reference.
* Model 2 adjusted for maternal age, race–ethnicity as a social determinant, method of payment, education level, trimester of prenatal care initiation, and parity.
† Model 3 additionally adjusted for validated obstetric comorbidity score. See text for details.
‡ Refer to text for details regarding categorization of epilepsy subtypes.
§ Cell sizes of fewer than 15 not shown per data-use agreement.

medications in this analysis, future research interrogating whether antiseizure medications affect the risk of SMM is warranted.

Strengths of our study include the large population, which enabled us to examine rare but clinically significant outcomes, and the pragmatic approach to associating epilepsy subtype with a standardized measure of maternal morbidity, which is applicable to clinical practice. These results can help risk-stratify patients and provide guidance for future research on risk mitigation strategies. Additionally, our analysis demonstrates that patients with epilepsy have higher rates of comorbidities, which are also risk factors for SMM. Furthermore, the robustness of our results was confirmed using propensity score matching.

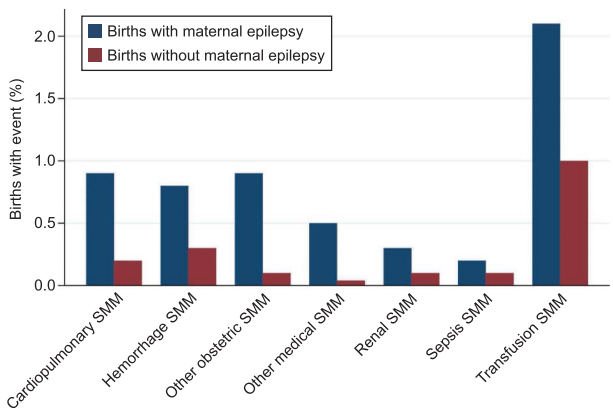

Fig. 2. Severe maternal morbidity (SMM) indicator event rates compared between births to patients with and without epilepsy in California, 2007–2012.

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Our results must be interpreted within the context of the study design and limitations. Though timing of events was not available retrospectively, we attempted to address causality between epilepsy and SMM by restricting only to epilepsy codes present at admission. There likely remain unmeasured confounders that were not accounted for or were not included due to concerns about coding reliability (eg, smoking status, cesarean indication, or epilepsy disease control). Owing to data-use agreements, we are unable to report rates of very rare outcomes, such as maternal mortality. Though our results may not be generalizable to populations outside of California, California is diverse and accounts for the greatest total number of births in the United States.[29]

In conclusion, the risk of SMM and nontransfusion SMM was significantly increased among patients with epilepsy, though, reassuringly, the absolute risks remain low.

REFERENCES

1. French JA, Kanner AM, Bautista J, Abou-Khalil A, Browne T, Harden CL, et al. Practice parameters, efficacy, and tolerability of the new antiepileptic drugs: treatment of new-onset epilepsy. Report of the TTA and QSS subcommittees of the American Academy of Neurology and the American Epilepsy Society. Epilepsia 2004;45:401–9. doi: 10.1111/j.0013-9580.2004.06204.x
2. Centers for Disease Control and Prevention. More Americans have epilepsy than ever before. Accessed February 25, 2019. https://www.cdc.gov/media/releases/2017/p0810-epilepsy-prevalence.html
3. Hessler A, Dolbec K. Seizures: clinical updates in women's health care primary and preventive care review. Obstet Gynecol 2021;137:207. doi: 10.1097/AOG.0000000000004211
4. MacDonald SC, Bateman BT, McElrath TF, Hernández-Díaz S. Mortality and morbidity during delivery hospitalization among

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pregnant women with epilepsy in the United States. JAMA Neurol 2015;72:981–8. doi: 10.1001/jamaneurol.2015.1017

5. Leach J, Smith P, Craig J, Bagary M, Cavanagh D, Duncan S, et al. Epilepsy and pregnancy: for healthy pregnancies and happy outcomes. Suggestions for service improvements from the Multispecialty UK Epilepsy Mortality Group. Seizure 2017;50:67–72. doi: 10.1016/j.seizure.2017.05.004
6. Viale L, Allotey J, Cheong-See F, Arroyo-Manzano D, Mccorry D, Bagary M, et al. Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis. Lancet 2015;386:1845–52. doi: 10.1016/S0140-6736(15)00045-8
7. Stephen LJ, Harden C, Tomson T, Brodie MJ. Management of epilepsy in women. Lancet Neurol 2019;18:481–91. doi: 10.1016/S1474-4422(18)30495-2
8. Edey S, Moran N, Nashef L. SUDEP and epilepsy-related mortality in pregnancy. Epilepsia 2014;55:72–4. doi: 10.1111/epi.12621
9. Harden CL, Hopp J, Ting TY, Pennell PB, French JA, Hauser WA, et al. Practice parameter update: management issues for women with epilepsy–focus on pregnancy (an evidence-based review): obstetrical complications and change in seizure frequency: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology 2009;73:126–32. doi: 10.1212/WNL.0b013e3181a6b2f8
10. Main EK, Abreo A, McNulty J, Gilbert W, McNally C, Poeltler D, et al. Measuring severe maternal morbidity: validation of potential measures. Am J Obstet Gynecol 2016;214:643.e1–10. doi: 10.1016/j.ajog.2015.11.004
11. Main EK. Reducing maternal mortality and severe maternal morbidity through state-based quality improvement initiatives. Clin Obstet Gynecol 2018;61:319–31. doi: 10.1097/GRF.0000000000000361
12. Centers for Disease Control and Prevention. Appendix 2. Severe maternal morbidity indicators and corresponding ICD codes during delivery hospitalizations. Accessed March 11, 2019. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/smm/severe-morbidity-ICD.htm
13. Leonard SA, Kennedy CJ, Carmichael SL, Lyell DJ, Main EK. An expanded obstetric comorbidity scoring system for predicting severe maternal morbidity. Obstet Gynecol 2020;136:440–9. doi: 10.1097/AOG.0000000000004022
14. Razaz N, Tomson T, Wikström AK, Cnattingius S. Association between pregnancy and perinatal outcomes among women with epilepsy. JAMA Neurol 2017;74:983–91. doi: 10.1001/jamaneurol.2017.1310
15. Baumeister L, Marchi K, Pearl M, Williams R, Braveman P. The validity of information on "race" and "Hispanic ethnicity" in California birth certificate data. Health Serv Res 2000;35:869–83.
16. Bateman BT, Mhyre JM, Hernandez-Diaz S, Huybrechts KF, Fischer MA, Creanga AA, et al. Development of a comorbidity index for use in obstetric patients. Obstet Gynecol 2013;122:957–65. doi: 10.1097/AOG.0b013e3182a603bb
17. Easter SR, Bateman BT, Sweeney VH, Manganaro K, Lassey SC, Gagne JJ, et al. A comorbidity-based screening tool to predict severe maternal morbidity at the time of delivery. Am J Obstet Gynecol 2019;221:271.e1–10. doi: 10.1016/j.ajog.2019.06.025
18. Ho DE, King G, Stuart EA, Imai K. MatchIt: nonparametric preprocessing for. J Stat Softw 2011;42:1–28.
19. Borthen I, Eide MG, Daltveit AK, Gilhus NE. Obstetric outcome in women with epilepsy: a hospital-based, retrospective study. BJOG 2011;118:956–65. doi: 10.1111/j.1471-0528.2011.03004.x
20. Melikova S, Bagirova H, Magalov S. The impact of maternal epilepsy on delivery and neonatal outcomes. Child's Nerv Syst 2020;36:775–82. doi: 10.1007/s00381-019-04435-2
21. Marson AG, Appleton R, Baker GA, Chadwick DW, Doughty J, Eaton B, et al. A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial. Health Technol Assess 2007;11:iii–iv, ix–x, 1–134. doi: 10.3310/hta11370
22. French JA, Gazzola DM. New generation antiepileptic drugs: what do they offer in terms of improved tolerability and safety? Ther Adv Drug Saf 2011;2:141–58. doi: 10.1177/2042098611411127
23. Kim H, Faught E, Thurman DJ, Fishman J, Kalilani L. Antiepileptic drug treatment patterns in women of childbearing age with epilepsy. JAMA Neurol 2019;94304:1–8. doi: 10.1001/jamaneurol.2019.0447
24. Meador KJ, Pennell PB, May RC, Gerard E, Kalaydjian L, Velez-Ruiz N, et al. Changes in antiepileptic drug-prescribing patterns in pregnant women with epilepsy. Epilepsy Behav 2018;84:10–4. doi: 10.1016/j.yebeh.2018.04.009
25. Veroniki AA, Cogo E, Rios P, Al E. Comparative safety of antiepileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes. BMC Med 2017;15:1–20. doi: 10.1186/s12916-017-0845-1
26. Meador KJ, Loring DW. Developmental effects of antiepileptic drugs and the need for improved regulations. Neurology 2016;86:297–306. doi: 10.1212/WNL.0000000000002119
27. Vajda FJE, Hollingworth S, Graham J, Hitchcock AA, O'Brien TJ, Lander CM, et al. Changing patterns of antiepileptic drug use in pregnant Australian women. Acta Neurol Scand 2010;121:89–93. doi: 10.1111/j.1600-0404.2009.01260.x
28. Vajda F, O'Brien T, Graham J, Hitchcock A, Lander C, Eadie M. Anti-epileptic drug exposure and risk of foetal death in utero. Acta Neurol Scand 2017;137:20–3. doi: 10.1111/ane.12816
29. Martin J, Hamilton B, Osterman M, Driscoll A. Births: final data for 2019. Natl Vital Stat Rep 2021;70:1–51.

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