The Canadian Journal of Neurological Sciences (2024), **51**, 397–403
doi:10.1017/cjn.2023.254

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Original Article

Obstetrical Outcomes of Patients with Epilepsy in a Canadian Tertiary Care Center (2014–2020)

Julien Hébert[1,2], Yajur Iyengar[3], Sharon Ng[4], Jenny Liao[3], John W. Snelgrove[5,6] and Esther Bui[1,4]

[1]Division of Neurology, University of Toronto, Toronto, ON, Canada, [2]Comprehensive Epilepsy Center, Columbia University Medical Center–New York Presbyterian Hospital, New York, NY, USA, [3]Faculty of Medicine, University of Toronto, Toronto, ON, Canada, [4]Toronto Western Hospital, University Health Network, Toronto, ON, Canada, [5]Department of Obstetrics & Gynaecology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada and [6]Institute of Health Policy, Management & Evaluation, University of Toronto, Toronto, ON, Canada

ABSTRACT: ***Background:*** There is a paucity of data on the obstetrical outcomes of Canadian pregnant patients with epilepsy, which may differ from the average Canadian pregnancy and from other populations of pregnant patients with epilepsy. ***Methods:*** Pregnant patients with epilepsy were identified from a prospectively collected database of patients seen at the maternal-fetal medicine obstetrics program of Mount Sinai Hospital (Toronto, Canada) between January 1, 2014, and November 20, 2020. Pregnancy, delivery, and neonatal outcome data were retrieved from this database and described using 95% binomial confidence intervals. Comparisons of obstetrical outcomes over the same period among the Canadian population average, obtained from publicly available national health data, were done using one-proportion Z-tests for nominal variables and one-sample t-tests for continuous variables. ***Results:*** In total, 282 pregnancies, from 224 patients, were included, which resulted in 274 live births. Mean maternal age was 32.8 years (*s.d.* = 4.6; population average [μ] = 30.9; $p < 0.01$), and 53% were primiparous ($CI_{95\%}$ = 49%–61%; μ = 43%; $p < 0.01$). The observed rates of obstetrical complications were gestational hypertension 9% ($CI_{95\%}$=6%–13%; μ=7%; p=0.19), gestational diabetes 5% ($CI_{95\%}$ = 3%–8%; μ = 9%; $p = 0.02$), cesarean section 44% ($CI_{95\%}$ = 38%–50%; μ = 28%; $p < 0.01$), postpartum hemorrhage 5% ($CI_{95\%}$ = 3%–8%; μ = 0.5%; $p < 0.01$), stillbirth 1% ($CI_{95\%}$ = 0%–2%; μ=1%; $p > 0.99$), and prematurity 9% ($CI_{95\%}$ = 6%–13%; μ = 8%; $p = 0.44$). ***Conclusion:*** In this cohort of Canadian pregnant patients with epilepsy from an urban tertiary care center, observed rates of obstetrical complications were rare and no higher than in the Canadian population over the same period, with the exception of cesarean section and postpartum hemorrhage. Future prospective studies that include primary care and rural settings are needed to increase the generalizability of those results.

RÉSUMÉ : Résultats obstétricaux chez des femmes enceintes, atteintes d'épilepsie dans un centre de soins tertiaires au Canada (2014-2020). ***Contexte :*** Il existe très peu de données sur les résultats obstétricaux observés chez les femmes enceintes, atteintes d'épilepsie au Canada, résultats qui peuvent différer de la moyenne enregistrée chez les femmes enceintes au pays et de ceux enregistrés dans d'autres populations de femmes enceintes, atteintes d'épilepsie. ***Méthode :*** Le repérage des femmes enceintes, atteintes d'épilepsie s'est fait dans une base de données, constituée de manière prospective, sur des femmes examinées à l'hôpital Mount Sinai, à Toronto (Canada), dans le cadre du programme d'obstétrique et de médecine materno-fœtale, entre le 1er janvier 2014 et le 20 novembre 2020. Les données recueillies sur la grossesse, l'accouchement et les résultats néonataux proviennent de cette base de données, et sont présentées selon des intervalles de confiance (IC) binomiaux, à 95 %. Des comparaisons, fondées sur des données nationales, publiques sur la santé, ont par la suite été établies entre les résultats obstétricaux enregistrés sur la même période, dans la population générale au Canada, à l'aide de tests Z à une proportion pour les variables nominales et de tests T à un échantillon pour les variables continues. ***Résultats :*** L'étude a porté sur 282 grossesses, touchant 224 patientes, qui ont donné lieu à 274 naissances vivantes. L'âge moyen des mères était de 32,8 ans (écart type : 4,6; âge moyen de la population générale [μ] : 30,9; $p < 0,01$) et 53 % d'entre elles étaient primipares (IC à 95 % : 49–61 %; μ : 43 %; $p < 0,01$). Les taux de complications obstétricales enregistrés dans l'étude s'établissaient comme suit : hypertension gravidique : 9 % (IC À 95 % : 6–13 %; μ : 7 %; p : 0,19); diabète gestationnel : 5 % (IC à 95 % : 3–8 %; μ : 9 %; p : 0,02); césarienne : 44 % (IC à 95 % : 38–50 %; μ : 28 %; $p < 0,01$); hémorragie de la délivrance : 5 % (IC à 95 % : 3–8 %; μ : 0,5 %; $p < 0,01$), mortinaissance :1 % (IC à 95 % : 0–2 %; μ : 1 %; $p > 0,99$) et prématurité : 9 % (IC à 95 % : 6–13 %; μ : 8 %; p : 0,44). ***Conclusion :*** D'après les résultats obtenus dans la cohorte de femmes enceintes, atteintes d'épilepsie (FEE) au Canada, dans un centre de soins tertiaires, en milieu urbain, les taux enregistrés de complications obstétricales étaient très bas et pas plus hauts que ceux relevés dans la population générale au Canada, au cours de la même période, à l'exception des césariennes et des hémorragies de la délivrance. La généralisation des résultats nécessite la réalisation d'autres études prospectives, notamment en centre de soins primaires et en milieu rural.

Keywords: epilepsy; clinical epidemiology; neuroepidemiology; obstetrics

(Received 25 January 2023; final revisions submitted 4 July 2023; date of acceptance 5 July 2023; First Published online 17 July 2023)

Corresponding author: E. Bui; Email: esther.bui@uhn.ca

Cite this article: Hébert J, Iyengar Y, Ng S, Liao J, Snelgrove JW, and Bui E. (2024) Obstetrical Outcomes of Patients with Epilepsy in a Canadian Tertiary Care Center (2014–2020). *The Canadian Journal of Neurological Sciences* **51**: 397–403, https://doi.org/10.1017/cjn.2023.254

Introduction

The prevalence of epilepsy during pregnancy has been estimated at 0.3%–0.7%.[1–9] Factors that make the care of pregnant patients with epilepsy (PPWE) distinct from pregnant patients without epilepsy (PPWoE) include the impact of seizures on maternal and fetal health,[10–15] the recognized changes in antiseizure medication (ASM) pharmacokinetic that occur during pregnancy,[16] and the possible teratogenicity of ASM,[16–18] which may be mitigated by the effects of folate supplementation on fetal development.[19] These factors must be reconciled with the recommendation that ASM be continued throughout pregnancy.[20]

PPWE also have unique demographics, when compared to PPWoE, higher rates of primiparity,[3,21,22] and a lower proportion of patients delivering at an advanced age[3,23] have both been reported. Additionally, PPWE were found to have higher rates of ectopic pregnancy,[21] hypertensive disorders of pregnancy,[5,24–30] preterm labor[2,21,24–26,29] spontaneous and therapeutic termination,[2,21,24,29] gestational diabetes,[4,21,31] cesarean section,[1,2,4,9,21,24–29,32] peripartum hemorrhage,[4,24,25,27,28,31] low neonatal birth weight,[2,3,9,22,24,29] postpartum depression,[33–35] and maternal mortality.[6,7,26] These findings were reported from studies performed in Scandinavia (Norway,[5,8,9,27] Finland,[21,23] Sweden,[28,36] Denmark,[7] Iceland),[1] the United Kingdom (UK),[31] the United States of America (USA),[3,6,25,26] Israel,[4] Thailand,[2] Taiwan,[32] and Canada.[30] Such increases in the rates of obstetrical complications have not been uniformly reported worldwide, however. For instance, while Iceland[1] and Finland[12,21] reported similar rates of gestational hypertension among PPWE, studies from the USA reported an increase in this obstetrical complication among PPWE.[25,26] In addition, a cohort study from the UK[31] did not replicate findings from Finland,[21,23] Norway,[5,9] and Thailand[2] showing increased rates of low-birth weight among the neonates of PPWE.

Given these cross-border variations, further Canadian-specific data are needed. In this study, we report the obstetrical outcomes of a cohort of Canadian PPWE receiving specialized obstetrical care in an urban tertiary care center in Toronto (ON).

Methods

Patient Selection and Data Collection

PPWE were identified from a preexisting prospectively collected database of patients seen in the maternal-fetal medicine obstetrics program at Mount Sinai Hospital (Toronto, ON, Canada) between January 1, 2014, and November 20, 2020. Epilepsy was defined according to the International League Against Epilepsy 2014 operational definition of epilepsy.[37]

The following data were collected through review of patients' records: *maternal demographics* (maternal age, level of education, ethnicity, prior deliveries, and births), *pregnancy data* (maternal smoking, folic acid supplementation, ASM usage in the first trimester, and termination of pregnancy, and diagnosis of gestational hypertension, diabetes, or bleeding), *delivery data* (use of instrumentation, mode of delivery, indications for cesarean section, as well as occurrence of and treatment received for postpartum hemorrhage), and *neonatal data* (stillbirth, prematurity, major congenital malformation, and Neonatal Intensive Care Unit admission). Patients who were lost to follow-up after a single maternal intake visit were excluded. A minimum of one six-week postpartum visit is considered standard of care in our institution. The following variables were obtained from Statistics Canada for all reported Canadian pregnancies between 2014 and 2020: maternal age, primiparity, gestational hypertension, gestational diabetes, cesarean delivery, postpartum hemorrhage, stillbirth, and prematurity. We performed a review of the English literature available in the PubMed database using the keywords "Epilepsy," "Pregnancy," and "Obstetrical outcomes" to retrieve studies on the obstetrical outcomes of Canadian PPWE.

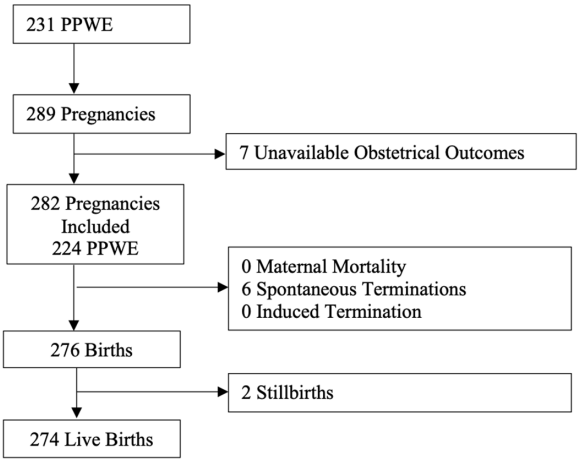

Figure 1: Study flowchart. PPWE=pregnant patients with epilepsy.

Statistical Analysis

Study sample characteristics were described using proportions and means with 95% confidence intervals. When comparing variables with the general Canadian population, we performed one-proportion Z-tests for nominal variables and one-sample T-tests for continuous variables. Multiple imputation, a statistical method that estimates the value of a missing variable based on other auxiliary variables available for a given patient, was performed with five iterations using the package *mice*.[38] Multiple imputation is favored against simply excluding the missing data, which is more likely to introduce censoring bias.[39] Statistical significance was determined as $p < 0.05$ unless otherwise specified. No correction for multiple comparisons was done due to the exploratory aims of this study. Study data were collected in REDCap (Research Electronic Data Capture).[40] Statistical analysis was performed with R Statistical Software version 4.1.2 (The R Foundation for Statistical Computing, 2021).

Ethical Conduct of Research

This study received approval from the Research Ethics Boards of Mount Sinai Hospital and the University Health Network (Toronto, ON, Canada).

Results

We identified 231 PPWE who had a total of 289 pregnancies (1.25 pregnancies per patient). Seven pregnancies from as many PPWE were excluded due to loss to follow-up (Fig. 1). Mean maternal age was 32.8 years (*stand. dev.* = 4.6). Most PPWEs were of white/European descent (Fig. 2a), married (Fig. 2b), and had some post-secondary education (Fig. 2c). Information on ethnicity was available in 67% (150/224) of patients, marital status in 90% (255/282) of pregnancies, and level of education in 57% (160/282) (Fig. 2d).

https://doi.org/10.1017/cjn.2023.254 Published online by Cambridge University Press

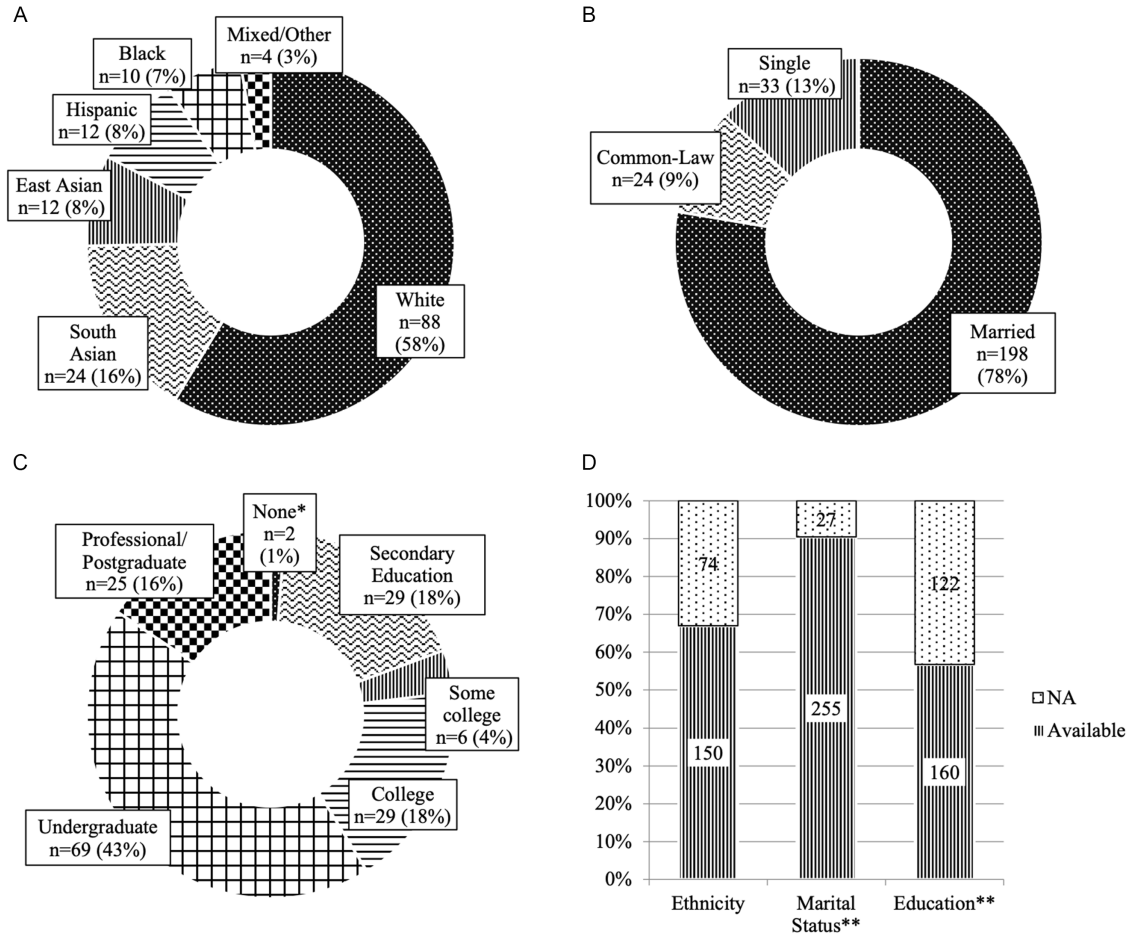

Figure 2: Demographic features of pregnant patients with epilepsy (Mount Sinai Hospital, Toronto, Canada, 2014–2020). ***a***) Ethnicity. ***b***) Marital status. ***c***) Educational achievement/degree. ***d***) Available data for each demographic variable. *No secondary education diploma/degree obtained. **Per pregnancy. NA=Not available.

A complete set of obstetrical outcome data was available for 74% of pregnancies (210/282). The variables with the largest proportion of missing data were admission to the neonatal intensive care unit (36/274; 13%), folic acid supplementation status (11%, 30/282), occurrence of stillbirth (7.6%; 21/276), major congenital malformation (6.9%; 19/274), or peripartum hemorrhage (6.5%; 18/276) (See Supplementary Material 1). The obstetrical outcomes of the cohort, after accounting for missing variables with multiple imputations, are summarized in Table 1.

Most pregnancies occurred in mothers who had previously been pregnant (35% primigravid, 98/282), but, in most cases, never previously had a live birth (55% primiparous, 150/274). Forty-five percent of deliveries were done by cesarean section (123/276), including 25% (30/123) electively (Fig. 3). While most cases of postpartum hemorrhage responded to uterotonics, a minority (29%, 4/14) required a combination of blood transfusion, mechanical tamponade, and surgical intervention. Nine newborns were found to have major congenital malformations: three congenital heart defects, one common truncus arteriosus, one transposition of the great arteries, one neural tube defect, one limb abnormality, and two non-specified congenital heart defects.

Compared with the average Canadian pregnancy during the same period, PPWEs from this cohort were older, more likely to be primiparous, and more likely to deliver via cesarean section and have postpartum hemorrhage. They had similar incidences of gestational hypertension, stillbirth, prematurity, and a lower incidence of gestational diabetes (Table 2).

In our cohort, 85% of pregnancies were uncomplicated (241/282, excluding peripartum vaginal bleeding). Ninety-three percent (257/276) of labor and deliveries were uncomplicated, and eighty-five percent (235/276) of newborns were born at term, free from major congenital malformation, and did *not* require Neonatal Intensive Care Unit admission. Altogether, 68% (193/282) of pregnancies were, therefore, uncomplicated and free from obstetrical or neonatal complications.

Our review of the existing literature on the obstetrical outcomes of Canadian PPWE yielded two studies, both from Montreal (QC): one by Richmond *et al.*[30] had a large sample size, which included a control group of PPWoE, and a second more recent by Li *et al.*[41] had a significantly smaller sample size and included a limited number of obstetrical outcome measures (Table 3).

Discussion

In our cohort of PPWE from an urban obstetrical tertiary care center, the majority had uncomplicated pregnancies and deliveries. Stillbirth and major congenital malformation were rare neonatal outcomes, occurring at rates similar to that observed in national pregnancy registries from other high-income countries,[5,9,24,28] and at a lower rate than previously reported in Canada between

https://doi.org/10.1017/cjn.2023.254 Published online by Cambridge University Press

Table 1: Obstetrical outcomes of patients with epilepsy in an urban tertiary care center (Mount Sinai Hospital, Toronto, Canada, 2014–2020)

	n	%	Confidence interval$_{95\%}$
Pregnancy			
Pregnancies	282	100	
Maternal age (years)	32.8[a]	4.6[b]	32.2–33.3
Primiparity	150	55	49–61
Maternal smoking	14	5	3–8
Folic acid intake	206	73	67–78
Gestational hypertension	25	9	6–13
Gestational diabetes	14	5	3–8
Delivery outcomes			
Births	276	100	
Caesarean delivery	123	45	38–50
Instrumental delivery[c]	21	8	5–11
Postpartum hemorrhage	14	5	3–8
Stillbirth	2	1	0–2
Neonatal outcomes			
Live births	274	100	
Admission to NICU	18	7	4–10
Preterm[d]	26	9	6–13
MCM	9	3	2–6

MCM=major congenital malformation; NICU=neonatal intensive care unit.
[a] Mean.
[b] Standard deviation.
[c] Forceps or vaccum.
[d] Gestational age at birth<37 weeks.

Table 2: Obstetrical outcomes of patients with epilepsy in an urban tertiary care center compared with the Canadian Population (2014–2020)

	Study cohort	Canadian population (μ)[a]	Comparison, *p*-value
Pregnancy			
Pregnancies, n	282	*NA*	
Maternal age, mean (*s.d.*), years	32.8 (4.6)	30.9[50]	<0.01**
Primiparity, n (%)	150 (55)	1,120,331 (43)[51]	<0.01**
Gestational hypertension, n (%)	25 (9)	*NA* (7)[52]	0.19
Gestational diabetes, n (%)	14 (5)	*NA* (9)[52]	0.02*
Delivery outcomes			
Births, n	276	2,650,709[49]	
Cesarean delivery, n (%)	123 (45)	*NA* (28)[42]	<0.01**
Postpartum hemorrhage, n (%)	14 (5)	*NA* (0.5)[53]	<0.01**
Stillbirth, n (%)	2 (1)	21,853 (1)	>0.99
Neonatal outcomes			
Live Births, n	274	2,628,856[49]	
Preterm, n (%)	26 (9)	*NA* (8)	0.44

s.d.=standard deviation.
[a] For 2014–2020.
* $p < 0.05$.
** $p < 0.01$.

1978–2000.[30] In contrast to these encouraging data, the rates of cesarean section and postpartum hemorrhage were higher than in the general Canadian population.[42] The rate of cesarean section in our cohort of PPWE (45%) was also higher than recently reported in studies of PPWE from Norway (21%),[9] Sweden (23%),[36]and the USA (37%).[25] This was also reflected in a higher rate of postpartum hemorrhage (5%) than reported in the USA (3%),[25] but similar to that reported in Sweden (5%).[36] The observed rate of cesarean section in our cohort of PPWE was also higher than previously reported among Canadian PPWE between 1978 and 2000.[30] The incidence of deliveries by cesarean section has increased in the overall Canadian population over the last two decades[42]; whether this increase has been more marked among PPWE than PPWoE remains to be clarified. Li *et al.* did not report on cesarean section rate in their more recent study.[41] It is, furthermore, difficult to ascertain whether the higher rate of cesarean section observed in our cohort is representative of the overall Canadian PPWE population or, if instead, it is applicable only to the narrower subgroup of PPWE seen in tertiary care centers (i.e., referral bias). For example, the higher proportion of cesarean section may have been due to the higher maternal age of patients referred to our center, a known risk factor for cesarean section, rather than

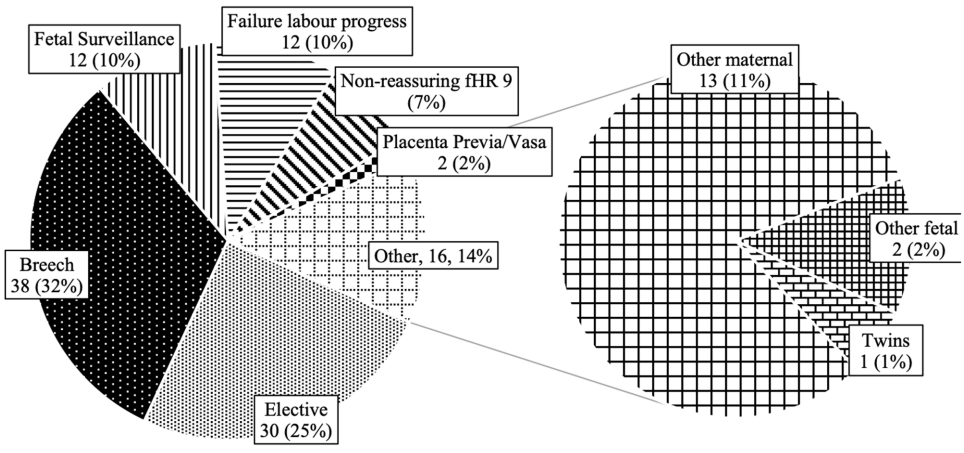

Figure 3: Indications for cesarean section delivery in pregnant patients with epilepsy (Mount Sinai Hospital, Toronto, Canada, 2014–2020). fHR=fetal heart rate.

https://doi.org/10.1017/cjn.2023.254 Published online by Cambridge University Press

Table 3: Canadian studies on obstetrical outcomes of patients with epilepsy

	Hébert et al. 2023	*Richmond et al. 2004*[30]	*Li et al. 2021*[41]
Study Characteristics			
City, Province	Toronto, ON	Montreal, QC	Montreal, QC
Period of inclusion	2014–2020	1978–2000	2003–2021
Single center	Yes	Yes	Yes
Tertiary care center	Yes	Yes	Yes
Study entry point	Seen at the Special Pregnancy Program at Mount Sinai	Delivered at the Royal Victoria Hospital	Seen by the epileptologist conducting the study
Sample size, n (PPWE)	224	313	53
Pregnancies, n (births)	289	414	72
Control group, n (births)	0	81,759	0
Pregnancy			
Age, mean (*s.d.*), yr	32.8 (4.6)	29.3 (5.1)	29 (NA)
Primiparity, n (%)	150 (53)	145 (35)	39 (54)
Gestational hypertension, n (%)	25 (9)	47 (11)	NA
Gestational diabetes, n (%)	14 (5)	17 (4)	NA
Folic acid supplementation, n (%)	206[a] (73)	286 (69)	50 (76)
Gestational bleeding, n (%)	64 (22)	49 (11)	NA
Delivery outcomes			
Spontaneous termination, n (%)	6 (2)	NA	8 (11)
Cesarean delivery, n (%)	123 (44)	100 (24)	NA
Instrumental delivery, n (%)	21 (8)	46 (11)	NA
Stillbirth, n (%)	2 (0.7)	1 (0.2)	NA
Neonatal outcomes			
Preterm, n (%)	26 (9)	43 (11)	NA
Major congenital malformation, n (%)	9 (3.4)	26 (6.3)	1 (2)

NA=not available; PPWE=pregnant patients with epilepsy; *s.d.*=standard deviation.

representing a true increase in the rates of cesarean section among PPWEs.

The mean maternal age of our cohort was indeed older than more recent studies of PPWE from Canada,[41] the USA,[43] and Finland.[21] Canadian PPWE may have delayed pregnancies to a larger extent than the general Canadian pregnant population, although we cannot exclude that this older maternal age is due to referral bias. Interestingly, Richmond *et al.* previously reported no such differences in maternal age between Canadian PPWE (mean age: 29.3 years) and PPWoE (mean age: 29.2).

In the approximately two-thirds of patients for whom data on ethnicity could be retrieved, 42% of our study participants were of non-white/European descent. By comparison, in the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs study, which took place in 20 epilepsy centers in the USA with a special focus on treating PPWE, the proportion of non-white/European patients was only 15%.[44] We could not retrieve comparable data on ethnicity for the overall Canadian pregnant population.

The high rate of primiparity (first live birth) observed in our cohort (53%) is consistent with observations among other studies of Canadian PPWE.[30,41] It is, however, higher than recently reported among PPWE in Sweden (36.4%)[36] and Norway (44.5%).[9] This may be due to patients with epilepsy choosing to have smaller families because of, real or perceived, safety concerns and unease about "transmitting" epilepsy to their children. Delays in having a first child may also be engendered by the need to optimize ASM regimen before conception. Again, referral bias may play a role in the observed high rates of primiparity in our cohort, with patients who previously experienced difficulties conceiving being more likely to attend a tertiary obstetrical care center.

When compared with the only Canadian study reporting on this outcome among PPWE, the rates of gestational hypertension and diabetes were similar in our cohort.[30] The proportion of active smokers observed in our cohort (5%) was lower than the population average among women of childbearing age during the same period (14%).[45,46] Whether this reflects a lower incidence of smoking in PPWE when compared with PPWoE, or a more widespread practice of tobacco weaning upon planning pregnancy is difficult to ascertain. Prior data in the general Canadian pregnant population indeed showed lower rates of smoking among pregnant patients than in the general population of women of childbearing age.[47,48] Maternal smoking prevalence in PPWE was not reported in the two aforementioned Canadian studies of PPWE.[30,41]

More patients were taking folic acid in our cohort than previously reported by Richmond *et al.* in 2004,[30] but less than

https://doi.org/10.1017/cjn.2023.254 Published online by Cambridge University Press

recently reported by Li *et al.*[41] in 2021 from their cohort of patients seen by a single epileptologist at a specialized epilepsy program. This suggests an increased awareness of the role of folic acid supplementation since 2004, and the possible benefits of follow-up with specialized epilepsy care.

Limitations

Our cohort of patients was selected from an urban obstetrical tertiary care center via a high-risk pregnancy clinical program; our results may not be generalizable to the overall Canadian population of PPWE, especially PPWE living in rural settings whose care may be more likely to be provided by a primary care provider. Due to the primary obstetrical focus of the source database for this study, epilepsy-specific data (e.g., ASM usage and epilepsy type) were not available. A prospective study design may allow more comprehensive data collection. In particular, data on ethnicity, folic acid supplementation, or whether pregnancies were planned or unplanned could be collected prospectively. Finally, future studies should consider including a control group of PPWoE within their design rather than relying on population-based data, to avoid potential biases introduced when comparing outcomes from heterogenous populations.

Conclusions

In this cohort of Canadian PPWE from an urban tertiary care center, observed rates of obstetrical complications were low and, with the exception of cesarean section and postpartum hemorrhage, no higher than the average Canadian pregnancy over the same period. Future prospective studies are needed to complete a more accurate representation of the obstetrical care and outcomes of Canadian PPWE.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/cjn.2023.254.

Competing interests. JH received salary support during his work on this study through a grant from the American Epilepsy Society. YI received a Women's Health Bursary from the University of Toronto for his work on this study. There are no other conflicts of interest to report.

Statement of authorship. JH: Study conception and design, analysis and interpretation of data, manuscript drafting and revising.

YI: Data collection and interpretation, manuscript drafting and revising.

SN: Data collection and interpretation, manuscript revising.

JL: Data collection and interpretation, manuscript revising.

JS: Study conception and design, interpretation of data, critical manuscript revising.

EB: Study conception and design, interpretation of data, critical manuscript revising, funding acquisition.

References

1. Olafsson E, Hallgrimsson JT, Hauser WA, Ludvigsson P, Gudmundsson G. Pregnancies of women with epilepsy: a population-based study in Iceland. Epilepsia. 1998;39:887–92.
2. Soontornpun A, Choovanichvong T, Tongsong T. Pregnancy outcomes among women with epilepsy: a retrospective cohort study. Epilepsy Behav. 2018;1:52–6.
3. Yerby M, Koepsell T, Daling J. Pregnancy complications and outcomes in a cohort of women with epilepsy. Epilepsia. 1985;26:631–5.
4. Katz O, Levy A, Wiznitzer A, Sheiner E. Pregnancy and perinatal outcome in epileptic women: a population-based study. J Matern Fetal Neonatal Med. 2006 Jan;19:21–5.
5. Danielsson KC, Borthen I, Morken NH, Gilhus NE. Hypertensive pregnancy complications in women with epilepsy and antiepileptic drugs: a population-based cohort study of first pregnancies in Norway. BMJ Open. 2018;8:e020998.
6. Edey S, Moran N, Nashef L. SUDEP and epilepsy-related mortality in pregnancy. Epilepsia. 2014;55:e72–74.
7. Christensen J, Vestergaard C, Hammer Bech B. Maternal death in women with epilepsy: smaller scope studies. Neurology. 2018;91:e1716–20.
8. Danielsson KC, Gilhus NE, Borthen I, Lie RT, Morken NH, Lupattelli A. Maternal complications in pregnancy and childbirth for women with epilepsy: Time trends in a nationwide cohort. PLoS ONE. 2019;14:e0225334.
9. Farmen AH, Grundt JH, Nakling JO, Mowinckel P, Nakken KO, Lossius MI. Increased rate of acute caesarean sections in women with epilepsy: results from the Oppland perinatal database in Norway. Eur J Neurol. 2019;26:617–23.
10. Kaplan PW, Norwitz ER, Ben-Menachem E, et al. Obstetric risks for women with epilepsy during pregnancy. Epilepsy Behav. 2007;11:283–91.
11. Sveberg L, Svalheim S, Taubøll E. The impact of seizures on pregnancy and delivery. Seizure. 2015;28:35–8.
12. Hiilesmaa VK, Bardy A, Teramo K. Obstetric outcome in women with epilepsy. Am J Obstet Gynecol. 1985;152:499–504.
13. Minkoff H, Schaffer RM, Delke I, Grunebaum AN. Diagnosis of intracranial hemorrhage in utero after a maternal seizure. Obstet Gynecol. 1985;65:22S–24S.
14. Chen YH, Chiou HY, Lin HC, Lin HL. Affect of seizures during gestation on pregnancy outcomes in women with epilepsy. Arch Neurol. 2009;66:979–84.
15. Adab N, Kini U, Vinten J, et al. The longer term outcome of children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry. 2004;75:1575–83.
16. Nau H, Zierer R, Spielmann H, Neubert D, Ch Gansau. A new model for embryotoxicity testing: teratogenicity and pharmacokinetics of valproic acid following constant-rate administration in the mouse using human therapeutic drug and metabolite concentrations. Life Sci. 1981;29:2803–13.
17. Robert E, Guibaud P. Maternal valproic acid and congenital neural tube defects. Lancet. 1982;320:937.
18. Tomson T, Battino D, Bonizzoni E, et al. EURAP: an international registry of antiepileptic drugs and pregnancy. Epilepsia. 2004;45:1463–4.
19. Tomson T, Battino D, Bromley R, et al. Management of epilepsy in pregnancy: a report from the international league against epilepsy task force on women and pregnancy. Epileptic Disord. 2019;21:497–517.
20. Harden CL, Meador KJ, Pennell PB, et al. Practice parameter update: management issues for women with epilepsy–focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes: report of the quality standards subcommittee and therapeutics and technology assessment subcommittee of the American academy of neurology and American epilepsy society. Neurology. 2009;73:133–41.
21. Artama M, Braumann J, Raitanen J, et al. Women treated for epilepsy during pregnancy: outcomes from a nationwide population-based cohort study. Acta Obstetricia et Gynecologica Scandinavica. 2017;96:812–20.
22. Viinikainen K, Heinonen S, Eriksson K, Kälviäinen R. Community-based, prospective, controlled study of obstetric and neonatal outcome of 179 pregnancies in women with epilepsy. Epilepsia. 2006;47:186–92.
23. Viinikainen K, Heinonen S, Eriksson K, Kalviainen R. Community-based, prospective, controlled study of obstetric and neonatal outcome of 179 pregnancies in women with epilepsy. Epilepsia. 2006;47:186–92.
24. Viale L, Allotey J, Cheong-See F, et al. Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis. The Lancet. 2015;386:1845–52.
25. Gyamfi-Bannerman C, Huang Y, Bateman BT, et al. Maternal morbidity and mortality associated with epilepsy. J Matern Fetal Neonatal Med. 2021;0:1–7.
26. MacDonald SC, Bateman BT, McElrath TF, Hernández-Díaz S. Mortality and morbidity during delivery hospitalization among pregnant women with epilepsy in the United States. Jama Neurol. 2015;72:981–8.

27. Borthen I, Eide M, Daltveit A, Gilhus N. Obstetric outcome in women with epilepsy: a hospital-based, retrospective study. BJOG Int J Obstet Gynaecol. 2011;118:956–65.
28. Pilo C, Wide K, Winbladh B. Pregnancy, delivery, and neonatal complications after treatment with antiepileptic drugs. Acta Obstet Gyn Scan. 2006;85:643–6.
29. Razaz N, Tomson T, Wikström AK, Cnattingius S. Association between pregnancy and perinatal outcomes among women with epilepsy. Jama Neurol. 2017;74:983–91.
30. Richmond JR, Krishnamoorthy P, Andermann E, Benjamin A. Epilepsy and pregnancy: an obstetric perspective. Am J Obstet Gynecol. 2004;190: 371–9.
31. Mawer G, Briggs M, Baker GA, et al. Pregnancy with epilepsy: obstetric and neonatal outcome of a controlled study. Seizure. 2010;19:112–9.
32. Yeh CC, Lussier EC, Sun YT, Lan TY, Yu HY, Chang TY. Antiepileptic drug use among women from the Taiwanese registry of epilepsy and pregnancy: obstetric complications and fetal malformation outcomes. PLoS ONE. 2017;12:e0189497.
33. H.Bjørk M, Veiby G, A.Engelsen B, Gilhus NE. Depression and anxiety during pregnancy and the postpartum period in women with epilepsy: a review of frequency, risks and recommendations for treatment. Seizure. 2015;28:39–45.
34. Turner K, Piazzini A, Franza A, et al. Postpartum depression in women with epilepsy versus women without epilepsy. Epilepsy Behav. 2006;9: 293–7.
35. Reiter SF, Veiby G, Daltveit AK, Engelsen BA, Gilhus NE. Psychiatric comorbidity and social aspects in pregnant women with epilepsy — the Norwegian mother and child cohort study. Epilepsy Behav. 2013;29:379–85.
36. Razaz N, Tomson T, Wikström AK, Cnattingius S. Association between pregnancy and perinatal outcomes among women with epilepsy. JAMA Neurol. 2017;74:983–91.
37. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55:475–82.
38. Buuren SV, Groothuis-Oudshoorn K. Mice: Multivariate Imputation by Chained Equations in *R*. J Stat Soft. 2011;45:1–67.
39. Madley-Dowd P, Hughes R, Tilling K, Heron J. The proportion of missing data should not be used to guide decisions on multiple imputation. J Clin Epidemiol. 2019;110:63–73.
40. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42:377–81.
41. Li J, Toffa DH, Nguyen DK. Epilepsy and pregnancy: an audit of specialized care. Can J Neurol Sci. 2022;49:678–87.
42. Statistics Canada. Labour and birth in Canada [Internet]. Ottawa: Public Health Agency of Canada; 2018, https://www.canada.ca/content/dam/hc-sc/documents/services/publications/healthy-living/maternity-newborn-care-guidelines-chapter-5/maternity-guidelines-chapter-5-en-info.pdf.
43. McElrath TF, Druzin ML, Van Marter LJ, et al. The obstetrical care and delivery experience of women with epilepsy in the MODEAD study. Am J Perinatol. 2022;1788–4791. doi: 10.1055/a-1788-4791
44. Pennell PB, French JA, May RC, et al. Changes in seizure frequency and antiepileptic therapy during pregnancy. N Engl J Med. 2020;383:2547–56.
45. Statistics Canada. Government of Canada SC. Population estimates on July 1st, by age and sex [Internet]. 2020. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710000501. Accessed February 6, 2021.
46. Statistics Canada. Health characteristics, annual estimates [Internet]. Government of Canada. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310009601. Accessed September 18, 2022.
47. Al-Sahab B, Saqib M, Hauser G, Tamim H. Prevalence of smoking during pregnancy and associated risk factors among Canadian women: a national survey. BMC Pregnancy Childbirth. 2010 Dec;10:24.
48. Erickson AC, Arbour LT. Heavy smoking during pregnancy as a marker for other risk factors of adverse birth outcomes: a population-based study in British Columbia. Canada BMC Public Health. 2012 Dec;12:102.
49. Statistics Canada. Live births and fetal deaths (stillbirths), by type of birth (single or multiple) [Internet]. Government of Canada. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310042801. Accessed September 18, 2022.
50. Statistics Canada. Mean age of mother at time of delivery (live births) [Internet]. Government of Canada. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310041701. Accessed September 17, 2022.
51. Statistics Canada. Live births, by age and parity of mother [Internet]. Government of Canada. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310042101. Accessed September 18, 2022.
52. Statistics Canada. Canadian chronic disease indicators data tool [Internet]. Ottawa (ON): Centre for Surveillance and Applied Research, Public Health Agency of Canada; 2019.
53. Statistics Canada. Postpartum health in Canada. Ottawa: Public Health Agency of Canada = Agence de la santé publique du Canada; 2020.

https://doi.org/10.1017/cjn.2023.254 Published online by Cambridge University Press