



Original Article

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

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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 ($CI_{95\%} = 49\%–61\%$; $\mu = 43\%$; $p < 0.01$). The observed rates of obstetrical complications were gestational hypertension 9% ($CI_{95\%} = 6\%–13\%$; $\mu = 7\%$; $p = 0.19$), gestational diabetes 5% ($CI_{95\%} = 3\%–8\%$; $\mu = 9\%$; $p = 0.02$), cesarean section 44% ($CI_{95\%} = 38\%–50\%$; $\mu = 28\%$; $p < 0.01$), postpartum hemorrhage 5% ($CI_{95\%} = 3\%–8\%$; $\mu = 0.5\%$; $p < 0.01$), stillbirth 1% ($CI_{95\%} = 0\%–2\%$; $\mu = 1\%$; $p > 0.99$), and prematurity 9% ($CI_{95\%} = 6\%–13\%$; $\mu = 8\%$; $p = 0.44$). **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 1^{er} 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

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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 Iceland¹ 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 UK³¹ did not replicate findings from Finland,^{21,23} Norway,^{5,9} and Thailand² 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:

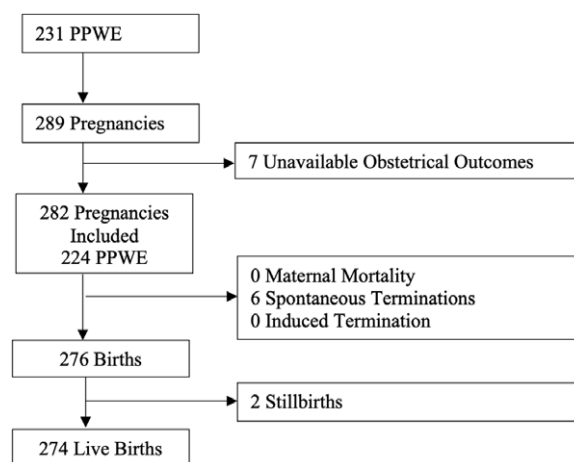


Figure 1: Study flowchart. PPWE=pregnant patients with epilepsy.

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.

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).

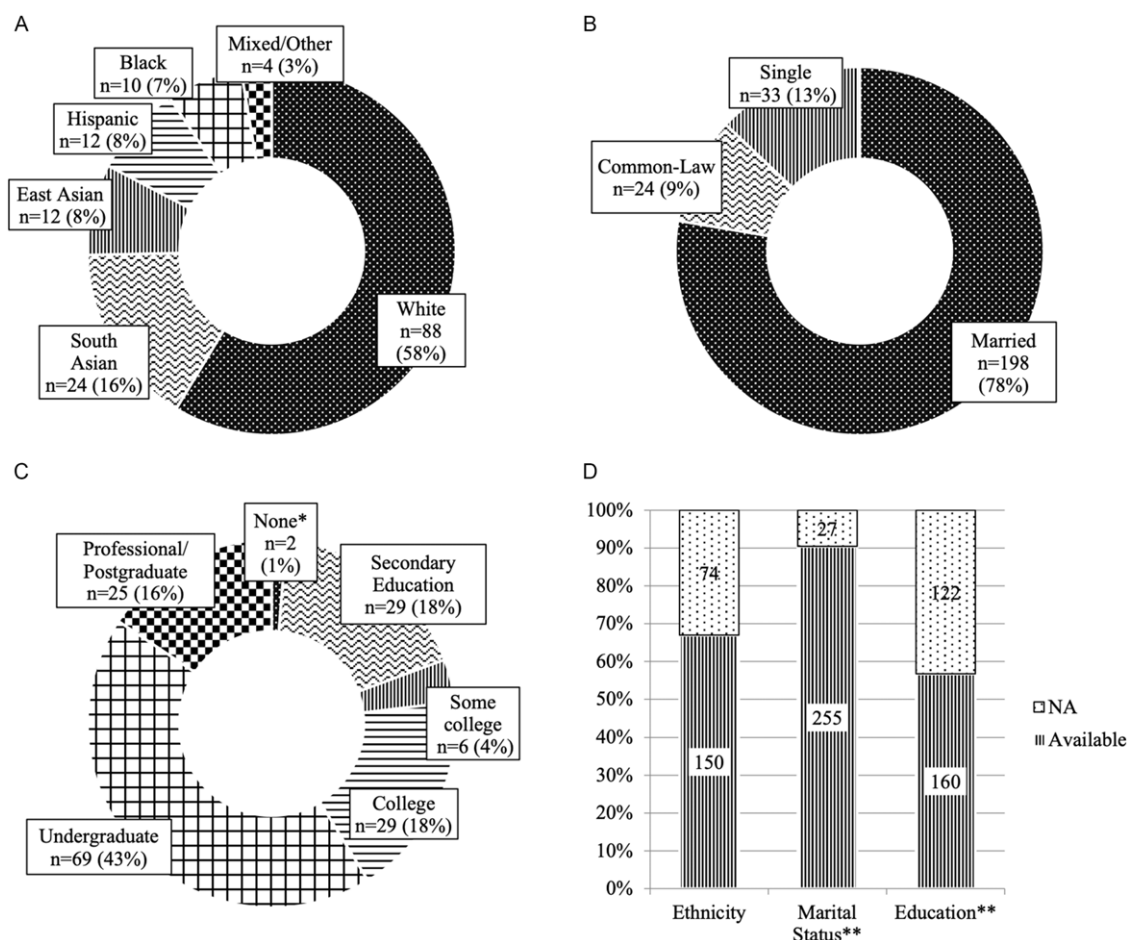


Figure 2: Demographic features of pregnant patients with epilepsy (Mount Sinai Hospital, Toronto, Canada, 2014–2020). **a)** Ethnicity. **b)** Marital status. **c)** Educational achievement/degree. **d)** Available data for each demographic variable. *No secondary education diploma/degree obtained. **Per 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 PPWE, 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

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

	<i>n</i>	%	Confidence interval _{95%}
<i>Pregnancy</i>			
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
<i>Delivery outcomes</i>			
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
<i>Neonatal outcomes</i>			
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 vacuum.^d Gestational age at birth<37 weeks.

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

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

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

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 decades⁴²; whether this increase has been more marked among PPWE than PPWE 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

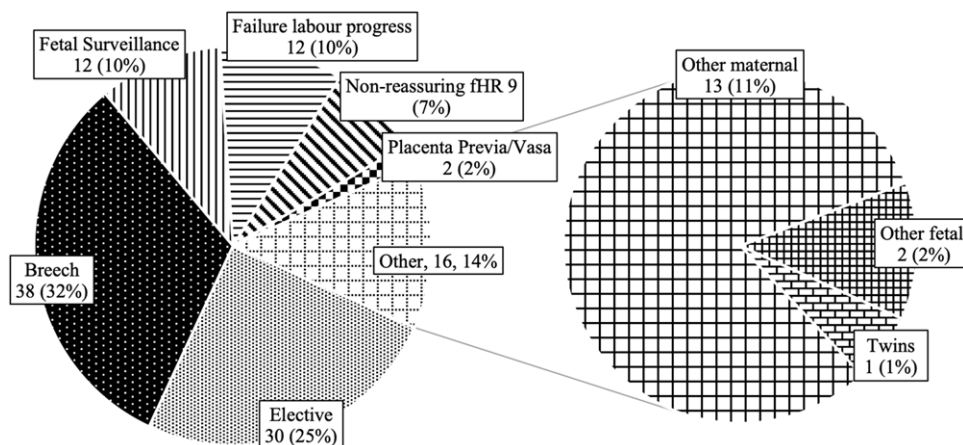
**Figure 3:** Indications for cesarean section delivery in pregnant patients with epilepsy (Mount Sinai Hospital, Toronto, Canada, 2014–2020). fHR=fetal heart rate.

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

	Hébert <i>et al.</i> 2023	Richmond <i>et al.</i> 2004 ³⁰	Li <i>et al.</i> 2021 ⁴¹
<i>Study Characteristics</i>			
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
<i>Pregnancy</i>			
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
<i>Delivery outcomes</i>			
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
<i>Neonatal outcomes</i>			
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

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 PPWE within their design rather than relying on population-based data, to avoid potential biases introduced when comparing outcomes from heterogeneous 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.

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