ORIGINAL ARTICLE

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Epilepsy and Pregnancy: An Audit of Specialized Care

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ABSTRACT: ***Background:*** Caring for women with epilepsy (WWE) during pregnancy poses unique challenges. We conducted an audit of the care our epilepsy clinic provided to pregnant WWE. ***Methods:*** We performed a retrospective study on all pregnancies followed by an epileptologist at a Canadian tertiary care centre's epilepsy clinic between January 2003 and March 2021. Among 81 pregnancies in 53 patients, 72 pregnancies in 50 patients were analyzed to determine patient-related, follow-up-related, antiseizure-medication-related, and child-related pregnancy characteristics. Univariate analyses were performed to explore if these characteristics were associated with disabling seizure occurrence during pregnancy. ***Results:*** Most pregnancies were intended (72%) and occurred in women who used folic acid pre-pregnancy (76%) and who followed recommended blood tests for antiseizure medication (ASM) levels (71%). In 49% of pregnancies, ASM dosage was modified; 53% of these modifications were made in response to ASM blood levels. Most often used ASMs were lamotrigine (43%), followed by carbamazepine (32%) and levetiracetam (13%). One child was born with a thyroglossal duct cyst; our congenital malformation rate was thus 2%. Disabling seizures occurred in 24% of pregnancies. Exploratory analyses suggested that disabling seizure occurrence during pregnancy was associated with younger patient age ($p = 0.018$), higher number of ASMs used during pregnancy ($p = 0.048$), lamotrigine usage in polytherapy ($p = 0.008$), and disabling seizure occurrence pre-pregnancy ($p = 0.027$). ***Conclusion:*** This Canadian audit provides an in-depth description of pregnancies benefiting from specialized epilepsy care. Our results suggest an association between disabling seizure occurrence during pregnancy and lamotrigine usage in polytherapy that warrants further evaluation.

RÉSUMÉ : Épilepsie et grossesse : un audit des soins spécialisés offerts. ***Contexte*** **:** La prise en charge des femmes épileptiques pendant leur grossesse pose des défis uniques. Nous avons donc effectué un audit des soins offerts à ces femmes par notre clinique de l'épilepsie. ***Méthodes*** **:** Pour ce faire, nous avons réalisé une étude rétrospective de toutes les grossesses suivies par un épileptologue dans notre clinique de l'épilepsie située dans un centre de soins tertiaires canadien, et ce, pour la période allant de janvier 2003 à mars 2021. Sur un total de 81 grossesses et de 53 patientes, 72 grossesses chez 50 patientes ont été analysées afin de déterminer les caractéristiques qui concernent les aspects suivants : les patientes elles-mêmes, les suivis effectués, la prise d'anticonvulsivants (AC) et le fœtus. Il est à noter que des analyses univariées ont été réalisées pour déterminer dans quelle mesure ces caractéristiques étaient associées en cours de grossesse à des crises convulsives invalidantes. ***Résultats*** **:** La majorité des grossesses étaient voulues (72 %). Qui plus est, elles se sont déroulées dans le cas de patientes qui, de façon majoritaire, avaient pris de l'acide folique avant leur grossesse (76 %) et qui avaient suivi les tests sanguins recommandés pour les niveaux d'AC (71 %). Pour 49 % des grossesses, le dosage des AC a dû être modifié ; 53 % de ces modifications ont été apportées en réponse aux niveaux sanguins d'AC. À ce propos, les AC les plus utilisés étaient la lamotrigine (43 %), la carbamazépine (32 %) ainsi que le lévétiracétam (13 %). Un enfant est né avec un kyste du tractus thyréoglosse (KTT). En cela, notre taux de malformation congénitale s'est établi à 2 %. Enfin, soulignons que des crises convulsives invalidantes sont survenues dans 24 % des grossesses. Des analyses exploratoires ont suggéré que l'apparition de telles crises en cours de grossesse était associée à des patientes plus jeunes ($p = 0{,}018$), à un plus grand nombre d'AC utilisés en cours de grossesse ($p = 0{,}048$), à l'utilisation de la lamotrigine dans le cadre d'une poly-thérapie ($p = 0{,}008$) ainsi qu'à l'apparition de crises convulsives invalidantes avant la grossesse ($p = 0{,}027$). ***Conclusion*** **:** Cet audit canadien fournit une description exhaustive des grossesses ayant bénéficié de soins spécialisés liés à l'épilepsie. Nos résultats suggèrent aussi une association entre l'apparition de crises convulsives invalidantes pendant la grossesse et la prise de lamotrigine dans le cadre d'une poly-thérapie, ce qui mérite une évaluation plus approfondie.

Keywords: Pregnancy, Audit, Epilepsy, Antiseizure medications, Seizure control, Congenital malformations

doi:10.1017/cjn.2021.190 Can J Neurol Sci. 2022; 49: 678–687

Introduction

Caring for women with epilepsy (WWE) during pregnancy poses unique challenges to the clinician. On one hand, it is widely established that many antiseizure medications (ASMs) can have undesirable effects on fetal development.[1] On the other hand, seizures occurring during pregnancy can harm both the mother and the fetus through various mechanisms such as blunt trauma.[2] In addition, pregnancy is accompanied by physiological changes

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Received May 29, 2021. Final Revisions Submitted July 15, 2021. Date of Acceptance July 30, 2021.

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https://doi.org/10.1017/cjn.2021.190 Published online by Cambridge University Press

that can affect the clearance of certain ASMs and thus cause their blood levels to fluctuate.[3] As such, latest international guidelines recommend periodically monitoring blood levels for ASMs that are most at risk of clearance changes during pregnancy.[4] Counterbalancing the inherent risk of using certain ASMs and the risk of seizure occurrence is essential for the proper care of the pregnant WWE.

Nevertheless, the optimal management of pregnant WWE is still under investigation, as many of the recommendations of latest guidelines are based on expert opinion rather than high quality evidence.[4] Recent publications have also challenged some traditionally well-accepted notions such as the usefulness of ASM level monitoring during pregnancy and the effects of pregnancy on seizure control.[5,6]

This study aims to investigate the overall quality of care our Canadian epilepsy centre provided to pregnant WWE by acting as an audit of clinical follow-up, maternal seizure control, and child outcomes. The findings of this audit will ultimately be used to better our services. Secondarily, this study aims to explore factors that may be associated with the occurrence of disabling epileptic seizures during pregnancy.

Methods

Patients

A retrospective study was performed on all pregnancies followed by an epileptologist at a Canadian academic tertiary care centre's outpatient epilepsy clinic (Montreal, Quebec) between January 2003 and March 2021. Pregnancies that were ongoing at the end of the study period were excluded. Pregnancies occurring in women who were followed at the time for suspected epilepsy but who were later retrospectively diagnosed with only psychogenic seizures were excluded as well. Out of 81 pregnancies in 53 patients, 72 pregnancies in 50 patients were included in the final analysis. This study was approved by our institution's ethics board as an audit project.

Clinical Practice

The recruiting epileptologist maintains a database of all patients seen at his epilepsy clinic, and all pregnancies occurring in these patients were prospectively identified throughout the 18-year study period by this epileptologist. From this database, these pregnancies were screened for study inclusion. Our epilepsy clinic is situated in an academic tertiary care centre and receives around 3000 visits per year. Five epileptologists work in this clinic. The epileptologist whose patients were screened for inclusion in this study dedicates 50% of his practice to research and received around 28% of all visits made to the clinic in 2020. In his practice, this epileptologist counseled all women of reproductive age on contraception use, pregnancy malformation risks, folic acid usage, and vitamin D usage. Pregnant women were further counselled on ASM level monitoring, breastfeeding, and post-natal care. When notified of a pregnancy, a prescription was sent to patients on lamotrigine, levetiracetam, oxcarbazepine, pregabalin and topiramate for monthly blood levels. For patients on carbamazepine and valproate, blood levels were ordered for each trimester. Upon reception of results, the epileptologist would decide if the ASM dose had to be increased or not. If changes were required, his epilepsy nurse would contact the patient to warn them of such a change and fax the prescription to the patient's pharmacy. As for any patient, pregnant WWE could contact the epilepsy nurse during working hours for epilepsy-related problems, such as to report seizures. Although in-person visits were possible for those who requested it, follow-ups during pregnancy were by telephone by default for the patient's convenience.

Regarding multidisciplinary care, obstetrical follow-up was ensured by obstetricians, primary care physicians, or internists. Pregnant patients would first look for obstetrical follow-up by contacting their primary care physician or by contacting a local hospital's obstetrical service. If a patient could not find a physician who could assure an obstetrical follow-up or if this patient desired to have an obstetrical follow-up at our institution, a consultation request was sent to our institution's obstetrical service. This service would then offer patients a follow-up in the high-risk pregnancy clinic or with internists specialized in obstetrical care. Modifications of ASM doses remained the epileptologist's responsibility. The clinical genetics service was consulted prior to pregnancy if genetic panel results yielded pathogenic results or variants of unknown significance.

Operational Definitions

A disabling seizure was defined as a seizure occurring with impaired awareness and/or resulting in a blunt trauma. Epilepsy type was defined as focal versus generalized and lesional versus non-lesional. Parity was defined as the number of a patient's previous pregnancies that had reached a viable gestational age. The postpartum period was defined as the three-month period following a live birth. Patients were considered to have "followed recommended blood tests for ASM levels" if at least two-thirds of their recommended ASM levels during pregnancy were received. This two-thirds threshold was chosen to account for variations in the timing at which patients would first announce their pregnancy to our staff. Pre-pregnancy folic acid usage was defined as the usage of 1 mg of folic acid daily at least three months before conception. A change in ASM type was considered to have occurred when an ASM was removed, added, or switched to another ASM during pregnancy.

Data Collection

Recorded data included the following:

a) patient-related characteristics (age at epilepsy onset, epilepsy type, post-surgery status, genetic panel results if available);
b) follow-up-related characteristics (year at which the pregnancy began, age at pregnancy, parity, whether or not the pregnancy was intended, contraception use, presence of specialized pre-pregnancy/early pregnancy counseling, whether or not the patient followed recommended blood tests for ASM levels, pre-pregnancy folic acid usage, whether or not the pregnancy was an urgent referral from another physician, concomitant high-risk pregnancy follow-up in obstetrics, number of in-person visits in clinic during pregnancy, number of telephone follow-ups during pregnancy excluding routine calls aimed at informing the patient of blood test results without making dose adjustments, presence of seizure complications, and presence of disabling seizures in the year preceding pregnancy, during pregnancy, and in the postpartum period);

https://doi.org/10.1017/cjn.2021.190 Published online by Cambridge University Press

c) ASM-related characteristics (number of ASMs used before/during pregnancy, changes in ASM type during pregnancy, changes in ASM dosage during pregnancy, whether or not these dosage modifications were directly due to ASM level monitoring, frequency of usage of each ASM);
d) and child-related characteristics (voluntary abortions, miscarriages, congenital malformations in the child, exposure to teratogenic substances during pregnancy other than ASMs, history of congenital malformations in previous offspring, autism spectrum disorder (ASD)).

Data were gathered by manually reviewing patient notes. Certain data (particularly child-related characteristics) were systematically collected by contacting the patients by telephone. Presence of ASD in a patient's child was determined through the patient's self-report during this systematic collection. Only children aged 2 years or older were considered for ASD, as diagnoses made at these ages have been suggested to be more reliable.[7]

Data Analysis

Data are presented as medians (interquartile range) for continuous variables and count (frequency) for proportions. Exploratory univariate comparisons between the subgroup of pregnancies occurring without disabling seizures and the subgroup of pregnancies occurring with disabling seizures were performed using non-parametric Mann-Whitney U tests for continuous variables and using Fisher's exact tests for proportions. As these univariate analyses were purely exploratory in nature, no correction for multiple comparisons was performed. Significance level was set at 0.05. Missing data were handled through pairwise deletion. All statistical analyses were performed using R version 4.02.[8]

Results

In total, 72 pregnancies in 50 patients were included in the final analysis. Tables 1–4 present the patient-related, follow-up-related, ASM-related, and child-related characteristics of all included pregnancies and furthermore compares many of these characteristics between two subgroups. The first subgroup was composed of the 54 pregnancies occurring in women who had no disabling seizures during pregnancy, whereas the second subgroup was composed of the 17 pregnancies occurring in women who had at least one disabling seizure during pregnancy. Table S1 presents additional information on lesional epilepsies, whereas Table S2 presents the detailed results of genetic panels.

Descriptive Analyses

Out of 72 pregnancies, three (4%) led to voluntary abortions, and eight (11%) led to miscarriages. All the voluntary abortions occurred during the first trimester and were not motivated by any knowledge of fetal abnormalities. Of the eight miscarriages, seven took place in the first trimester, and one in the third trimester. No pregnancies underwent invasive prenatal diagnostic procedures. Few pregnancies took place in women who had had epilepsy surgery in the past (10%) or who benefited from a genetic panel (18%). For most pregnancies, when a genetic panel was done, the results were normal (5/13 = 38%) or yielded variants of unknown significance (6/13 = 46%). Most pregnancies were "first" pregnancies (57%) in that they occurred in nulliparous women. Most pregnancies were intended (72%). Most pregnancies occurred in women who benefited from specialized counseling pre-pregnancy/early pregnancy (62%), who followed recommended blood tests for ASM levels (71%), and who were on folic acid pre-pregnancy (76%). A subset of pregnancies occurred despite the usage of a contraceptive method (19%), most often a condom (5/12 = 42%). Three pregnancies began as the patient was on an oral contraceptive pill (3/12 = 25%): one woman was taking valproate at pregnancy onset, another was taking lamotrigine, and the last was taking a combination of lamotrigine and oxcarbazepine. One pregnancy began in a patient who was taking phenytoin whilst using a vaginal ring (1/12 = 8%). The median number of in-person visits at our clinic during pregnancy was zero, whereas the median number of telephone follow-ups to make dose adjustments during pregnancy was two. Most pregnancies benefited from ASM monotherapy (61%). The most used ASMs during pregnancy in descending order were as follows: lamotrigine (43%), carbamazepine (32%), levetiracetam (13%), clobazam/oxcarbazepine (11%), valproate (6%), topiramate (4%), gabapentin/phenytoin/pregabalin (3%), and brivaracetam/lacosamide/phenobarbital/eslicarbazepine/clonazepam (1%). Changes in ASM type were occasionally made (10%), but these changes were not made in direct response to conclusions drawn using ASM level monitoring. On the other hand, changes in ASM dosage were frequent (49% of pregnancies, a total of 59 dose modifications with an average of two modifications per pregnancy), and most changes were made in direct response to findings from ASM level monitoring (53%). When pregnancies resulting in first trimester miscarriages and voluntary abortions are excluded, changes in ASM dosage become relatively more frequent (60% of pregnancies). Figure 1 presents the evolution of ASM usage in pregnancies occurring over the study period. Most pregnancies were free of disabling seizures 1 year before the pregnancy began (75%), during pregnancy (76%), and in the postpartum period (83%). One complication (1%) was noted in a patient: a postpartum status epilepticus. One congenital malformation (2%) – a thyroglossal duct cyst – was noted in the child of a patient who took carbamazepine during pregnancy. None of the patients took teratogenic substances other than ASMs during their pregnancy or had a history of congenital malformations in previous offspring. One child (2%) of a patient who took carbamazepine during pregnancy was diagnosed with ASD.

Exploratory Analyses

Exploratory univariate analyses showed that pregnancies in the second subgroup occurred in women who were significantly younger than in the first subgroup ($p = 0.018$). The number of ASMs used during pregnancy was significantly higher in the second subgroup compared to the first ($p = 0.048$). Lamotrigine usage was significantly more frequent in the second subgroup ($p = 0.011$), and this held true for lamotrigine usage in polytherapy ($p = 0.008$) but not as monotherapy ($p = 0.999$). Presence of at least one disabling seizure in the 1-year period before pregnancy was associated with disabling seizure occurrence during pregnancy ($p = 0.027$). All other comparisons between both subgroups yielded non-significant results, as can be noted in Tables 1–4.

https://doi.org/10.1017/cjn.2021.190 Published online by Cambridge University Press

Table 1: Patient-related pregnancy characteristics, including comparisons between two subgroups defined by disabling seizure occurrence during pregnancy

Variable	All pregnancies		Subgroup 1		Subgroup 2		p-value
	Value	N	Value	N_1	Value	N_2	
Age of onset of epilepsy in years, median (IQR)	16 (12,20)	71	17 (13,20)	53	16 (12,18)	17	0.995
Lesional epilepsy, n (%)	24 (35)	69	18 (35)	51	6 (35)	17	0.999
Focal epilepsy, n (%)	56 (78)	72	41 (76)	54	14 (82)	17	0.745
Post-epilepsy-surgery, n (%)	7 (10)	72	5 (9)	54	2 (12)	17	0.670
Genetic panel, n (%)	13 (18)	72	10 (19)	54	3 (18)	17	0.999
Normal genetic panel, n (%)	5 (38)	13	4 (40)	10	1 (33)	3	–
VUS, n (%)	6 (46)	13	6 (60)	10	0	3	–
Pathogenic mutations, n (%)	2 (15)	13	0	10	2 (67)	3	–

IQR = interquartile range; n = count; N = sample size; VUS = variant of unknown significance.
Subgroup 1 included pregnancies occurring in patients who had no disabling seizures during pregnancy.
Subgroup 2 included pregnancies occurring in patients who had disabling seizures during pregnancy.
P values were calculated using Fisher's exact tests or using Mann-Whitney U tests, when appropriate.

Discussion

This study sought to provide an in-depth description of pregnancies followed in our academic tertiary care centre's epilepsy clinic. In doing so, we aim to suggest improvements to our practice. We secondarily explored our audit data for associations between certain pregnancy characteristics and the occurrence of disabling seizures during pregnancy.

ASM Choice

ASM choice is a pivotal issue in pregnancy, as many ASMs have been shown to have adverse effects on the developing fetus and to undergo clearance changes during pregnancy.[1,3] In our cohort, the most frequently used ASMs in descending order were as follows: lamotrigine, carbamazepine, levetiracetam, and clobazam/oxcarbazepine. While considering only ASM monotherapies, the list would change as follows: lamotrigine, carbamazepine, levetiracetam, valproate, and oxcarbazepine. The North American Antiepileptic Drug Pregnancy Registry showed that in 2019 the most frequently used ASMs during pregnancy were levetiracetam, followed by lamotrigine, gabapentin, oxcarbazepine, zonisamide, and carbamazepine.[9] Our practice deviates most noticeably in terms of our frequent usage of carbamazepine and our somewhat infrequent usage of levetiracetam. Carbamazepine is traditionally accepted as carrying a teratogenic risk for neural tube defects, whereas lamotrigine and levetiracetam are accepted as the least teratogenic ASMs.[10,11] However, levetiracetam and lamotrigine are known to undergo clearance changes during pregnancy which can cause their blood levels to fluctuate significantly.[12,13] Carbamazepine levels, on the other hand, are believed to remain more stable throughout pregnancy.[13] Furthermore, although carbamazepine carries a 2.7% (95% CI 1.9–3.8%) risk of malformations in comparison with lamotrigine's 1.9% (95% CI 1.5–2.6%) and levetiracetam's 1.8% (95% CI 1.2–2.7%), these risks have not been shown to significantly differ from one another.[9] In our practice, carbamazepine is also much simpler to dose than lamotrigine and levetiracetam for logistical reasons. As a result, our ASM usage reflects an important theme in managing pregnant WWE: counterbalancing teratogenic risk with the stability of ASM levels. Although we would not suggest starting carbamazepine in WWE contemplating pregnancy, often we may face patients considering pregnancy who are already on carbamazepine and who have a well-controlled epilepsy. In these women, we believe it can be argued that preserving carbamazepine throughout pregnancy would be a reasonable choice as long as the patient's seizures remain well-controlled. As for the relatively infrequent usage of levetiracetam in our patients' pregnancies, our findings suggest this ASM has only become consistently used in our cohort from 2014 onwards. This trend could be explained by the logistical difficulty in obtaining levetiracetam levels and the fact that this ASM has traditionally been more expensive than some other ASMs in our province.[14,15] In the future, we should aim to orient our ASM choice more towards levetiracetam, especially if blood levels for this ASM can be more easily acquired. As further evidence is obtained on ASM malformation risks, we may stray farther from certain ASMs, such as carbamazepine, in favor of others.

ASM Level Monitoring

Another issue in the management of pregnant WWE is the blood level monitoring itself. A British trial challenged the usefulness of ASM level monitoring, showing no differences in seizure outcomes between two groups of pregnant WWE, one randomized to receive ASM level monitoring and the other randomized to only clinical monitoring. However, this trial did not manage to recruit enough patients to provide a definitive answer on the subject; in fact, power analyses estimated that 660 patients were required to demonstrate a 25% seizure hazard

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Table 2: Follow-up-related pregnancy characteristics, including comparisons between two subgroups defined by disabling seizure occurrence during pregnancy

Variable	All pregnancies		Subgroup 1		Subgroup 2		p-value
	Value	N	Value	N_1	Value	N_2	
Age at pregnancy in years, median (IQR)	29 (26, 33)	72	30 (27, 33)	54	27.0 (23, 29)	17	**0.018***
Parity, median (IQR)	0 (0, 1)	69	0 (0, 1)	53	0 (0, 1)	16	0.216
Pregnancy in nulliparous woman, n (%)	39 (57)	69	30 (60)	53	9 (56)	16	0.999
Intended pregnancy, n (%)	48 (72)	67	38 (72)	53	10 (71)	14	0.999
On contraception as pregnancy began, n (%)	12 (19)	64	8 (16)	50	4 (29)	14	0.438
Condom, n (%)	5 (42)	12	5 (63)	8	0	4	–
Oral contraceptive pill, n (%)	3 (25)	12	2 (20)	8	1 (25)	4	–
Intra-uterine device, n (%)	3 (25)	12	1 (13)	8	2 (50)	4	–
Vaginal ring, n (%)	1 (8)	12	0	8	1 (25)	4	–
Specialized counseling before pregnancy, n (%)	42 (62)	68	33 (62)	53	9 (60)	15	0.999
Followed recommended blood tests for ASM levels, n (%)	43 (71)	61	33 (73)	45	10 (63)	16	0.526
On folic acid before pregnancy, n (%)	50 (76)	66	39 (75)	52	10 (77)	13	0.999
Urgent referral from another physician, n (%)	5 (7)	70	4 (7)	54	1 (7)	15	0.999
Concomitant obstetrical follow-up for high-risk pregnancy, n (%)	19 (26)	72	13 (24)	54	6 (35)	17	0.365
In-person visits in clinic during pregnancy, median (IQR)	0 (0, 1)	72	0.5 (0, 1)	54	0 (0, 1)	17	0.528
Telephone follow-ups during pregnancy, median (IQR)	2 (1,2)	72	2 (1,2)	54	2 (1,3)	17	0.052
Presence of disabling seizure in one-year period before pregnancy, n (%)	18 (25)	72	10 (19)	54	9 (47)	17	**0.027***
Presence of disabling seizure during pregnancy, n (%)	17 (24)	71	–	–	–	–	–
Presence of disabling seizure in postpartum period, n (%)	10 (17)	58	–	–	–	–	–
Seizure complication, n (%)	1 (1)	70	1 (2)	53	0	17	0.999

ASM = antiseizure medication; IQR = interquartile range; n = count; N = sample size.
Subgroup 1 included pregnancies occurring in patients who had no disabling seizures during pregnancy.
Subgroup 2 included pregnancies occurring in patients who had disabling seizures during pregnancy.
P values were calculated using Fisher's exact tests or using Mann-Whitney U tests, when appropriate.
*$p < 0.05$.

decrease with ASM level monitoring, but ultimately only 267 patients were randomized.[5] A recent American cohort study found that seizure frequency did not significantly differ throughout pregnancy for WWE in comparison with non-pregnant epileptic controls who underwent a similar follow-up. However, the odds that WWE would receive ASM dose changes during pregnancy were approximately six times higher than for non-pregnant WWE. These findings may indirectly reflect the importance of ASM level monitoring, as perhaps pregnant WWE had less seizures precisely due to the more frequent ASM dose changes, which may have been brought on by ASM level monitoring.[6] In brief, ASM level monitoring during pregnancy is still a widely recommended practice, especially for ASMs that are at risk of major blood level fluctuations.[4,12]

In our audit, ASM dose modifications were made in 49% of pregnancies. This estimate should be interpreted with caution, as

https://doi.org/10.1017/cjn.2021.190 Published online by Cambridge University Press

Table 3: ASM-related pregnancy characteristics, including comparisons between two subgroups defined by disabling seizure occurrence during pregnancy

Variable	All pregnancies		Subgroup 1		Subgroup 2		p-value
	Value	N	Value	N_1	Value	N_2	
Number of ASM tried in total during lifetime, median (IQR)	4 (2,6)	72	4 (2,5)	54	5 (2,7)	17	0.384
Number of ASM stopped before pregnancy, median (IQR)	2 (1,4)	72	2.0 (1,4)	54	3 (1,5)	17	0.567
Number of ASM used during pregnancy, median (IQR)	1 (1,2)	72	1 (1,2)	54	2 (1,2)	17	**0.048***
ASM monotherapy during pregnancy, n (%)	44 (61)	72	36 (67)	54	8 (47)	17	0.164
ASM type change during pregnancy, n (%)	7 (10)	72	3 (6)	54	4 (24)	17	0.052
ASM dose change during pregnancy, n (%)	30 (49)	61	21 (46)	46	9 (60)	15	0.764
LTG usage, n (%)	31 (43)	72	18 (33)	54	12 (71)	17	**0.011***
LTG as monotherapy, n (%)	12 (17)	72	9 (17)	54	3 (18)	17	0.999
LTG in polytherapy, n (%)	19 (26)	72	9 (17)	54	9 (53)	17	**0.008***
CBZ usage, n (%)	23 (32)	72	19 (35)	54	4 (24)	17	0.554
CBZ as monotherapy, n (%)	8 (11)	72	8 (15)	54	0	17	0.185
CBZ in polytherapy, n (%)	15 (21)	72	11 (20)	54	4 (24)	17	0.745
LEV usage, n (%)	10 (13)	72	7 (13)	54	2 (12)	17	0.999
LEV as monotherapy, n (%)	7 (10)	72	6 (11)	54	1 (6)	17	0.999
LEV in polytherapy, n (%)	3 (4)	72	1 (2)	54	1 (6)	17	0.424
CLB usage, n (%)	8 (11)	72	7 (13)	54	1 (6)	17	0.670
CLB as monotherapy, n (%)	0	72	–	–	–	–	–
CLB in polytherapy, n (%)	8 (11)	72	7 (13)	54	1 (6)	17	0.670
OXC usage, n (%)	8 (11)	72	5 (9)	54	3 (18)	17	0.387
OXC as monotherapy, n (%)	2 (3)	72	2 (4)	54	0	17	0.999
OXC in polytherapy, n (%)	6 (8)	72	3 (6)	54	3 (18)	17	0.144
VPA usage, n (%)	5 (7)	72	4 (7)	54	1 (6)	17	0.999
VPA as monotherapy, n (%)	4 (6)	72	4 (7)	54	0	17	0.566
VPA in polytherapy, n (%)	1 (1)	72	0	54	1 (6)	17	0.239
TPM usage, n (%)	3 (4)	72	1 (2)	54	2 (12)	17	0.140
TPM as monotherapy, n (%)	1 (1)	72	0	54	1 (6)	17	0.239
TPM in polytherapy, n (%)	2 (3)	72	1 (2)	54	1 (6)	17	0.424
GPN usage, n (%)	2 (3)	72	2 (4)	54	0	17	0.999
GPN as monotherapy, n (%)	0	72	–	–	–	–	–
GPN in polytherapy, n (%)	2 (3)	72	2 (4)	54	0	17	0.999
PHT usage, n (%)	2 (3)	72	1 (2)	54	1 (6)	17	0.424
PHT as monotherapy, n (%)	1 (1)	72	0	54	1 (6)	17	0.239
PHT in polytherapy, n (%)	1 (1)	72	1 (2)	54	0	17	0.999
PGB usage, n (%)	2 (3)	72	2 (4)	54	0	17	0.999
PGB as monotherapy, n (%)	0	72	–	–	–	–	–
PGB in polytherapy, n (%)	2 (3)	72	2 (4)	54	0	17	0.999
BRV usage, n (%)	1 (1)	72	0	54	1 (6)	17	0.239
BRV as monotherapy, n (%)	0	72	–	–	–	–	–
BRV in polytherapy, n (%)	1 (1)	72	0	54	1 (6)	17	0.239
LCM usage, n (%)	1 (1)	72	0	54	1 (6)	17	0.239

https://doi.org/10.1017/cjn.2021.190 Published online by Cambridge University Press

Table 3: ***(Continued)***

Variable	All pregnancies		Subgroup 1		Subgroup 2		p-value
	Value	N	Value	N_1	Value	N_2	
LCM as monotherapy, n (%)	0	72	–	–	–	–	–
LCM in polytherapy, n (%)	1 (1)	72	0	54	1 (6)	17	0.239
Pb usage, n (%)	1 (1)	72	1 (2)	54	0	17	0.999
Pb as monotherapy, n (%)	0	72	–	–	–	–	–
Pb in polytherapy, n (%)	1 (1)	72	1 (2)	54	0	17	0.999
ESL usage, n (%)	1 (1)	72	1 (2)	54	0	17	0.999
ESL as monotherapy, n (%)	1 (1)	72	1 (2)	54	0	17	0.999
ESL in polytherapy, n (%)	0	72	–	–	–	–	–
CNZ usage, n (%)	1 (1)	72	1 (2)	54	0	17	0.999
CNZ as monotherapy, n (%)	0	72	–	–	–	–	–
CNZ in polytherapy, n (%)	1 (1)	72	1 (2)	54	0	17	0.999

ASM = antiseizure medication; BRV = brivaracetam; CBZ = carbamazepine; CLB = clobazam; CNZ = clonazepam; ESL = eslicarbazepine; GPN = gabapentin; IQR = interquartile range; LCM = lacosamide; LTG = lamotrigine; LEV = levetiracetam; n = count; N = sample size; OXC = oxcarbazepine; Pb = phenobarbital; PGB = pregabalin; PHT = phenytoin; RF = risk factor; TPM = topiramate; VPA= valproate.
Subgroup 1 included pregnancies occurring in patients who had no disabling seizures during pregnancy.
Subgroup 2 included pregnancies occurring in patients who had disabling seizures during pregnancy.
P values were calculated using Fisher's exact tests or using Mann-Whitney U tests, when appropriate.
*$p < 0.05$.

Table 4: Child-related pregnancy characteristics, including comparisons between two subgroups defined by disabling seizure occurrence during pregnancy

Variable	All pregnancies		Subgroup 1		Subgroup 2		p-value
	Value	N	Value	N_1	Value	N_2	
Voluntary abortion, n (%)	3 (4)	72	1 (2)	54	2 (12)	17	0.140
Miscarriage, n (%)	8 (11)	72	8 (15)	54	0	17	0.185
CM in child, n (%)	1 (2)	52	1 (3)	40	0	12	0.999
Other risk factors for CM in child, n (%)	0	52	–	–	–	–	–
ASD in child, n (%)	1 (2)	46	1 (3)	35	0	11	0.999

ASD = autism spectrum disorder; CM = congenital malformation; n = count; N = sample size.
Subgroup 1 included pregnancies occurring in patients who had no disabling seizures during pregnancy.
Subgroup 2 included pregnancies occurring in patients who had disabling seizures during pregnancy.
P values were calculated using Fisher's exact tests or using Mann-Whitney U tests, when appropriate.

it was calculated based on all pregnancies, including those which resulted in a first trimester miscarriage/abortion. Since these pregnancies terminated early, there was a lower likelihood that they would present instances of ASM dose changes. The recalculated proportion of ASM dose modifications when excluding these pregnancies was 60%. In total, 59 ASM dose modifications were made, yielding an average of two modifications per pregnancy. The absolute number of ASM dose modifications was in reality higher than 59, as some data were missing and were treated with pairwise deletion. In addition, immediate postpartum dose changes were not considered when generating this estimate. Nevertheless, of these 59 dose modifications, 53% were made directly in response to ASM blood levels being too low. This estimate may grossly be interpreted as a measure of relevance of ASM level monitoring itself. ASM dose changes were otherwise mostly made in response to patients presenting disabling seizures, though some changes were pre-emptively planned to be made in the beginning of pregnancy or requested by the patients themselves.

In 30% of pregnancies, at least two-thirds of the recommended blood tests were never received. This problem may be due to patient non-compliance to blood tests as well as to administrative issues related to the reception of results by our clinic. When we do receive ASM levels, the delay between blood sampling and result reception can be problematic; for instance, it takes around two weeks for lamotrigine levels to be received by our clinic due

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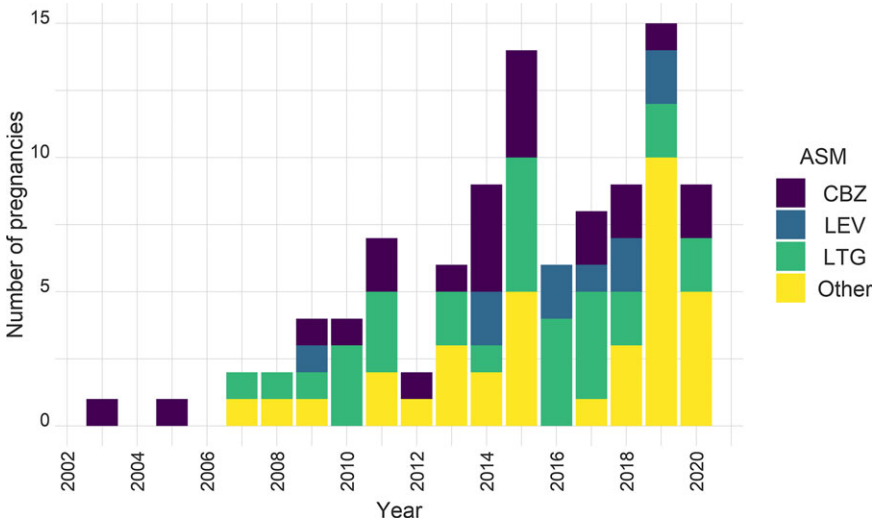

Figure 1: *Evolution of antiseizure medication usage throughout the study period. ASM = antiseizure medication; CBZ = carbamazepine; LTG = lamotrigine; LEV = levetiracetam. For a list of ASMs constituting the "other" category, the reader is invited to refer to Table 3. In this figure, we can observe a steady increase in the number of pregnancies followed at our clinic over the years. Lamotrigine usage and carbamazepine usage were first noted in 2007 and 2009, respectively. Usage of these two ASMs seems to have fluctuated with time. Similarly, levetiracetam usage was first noted in 2009 but appears to have only become consistent from 2014 onwards. Incidentally, 2019 featured the most frequent use of "other" ASMs, a finding which may be explained by the fact that most pregnancies occurring that year were on ASM polytherapy and that one woman exceptionally took a combination of four "other" ASMs (clobazam, oxcarbazepine, phenytoin, and phenobarbital) during pregnancy.*

to a suboptimized blood test delivery process. An example of this suboptimization can be seen in our province's method of "batch-processing" blood samples for lamotrigine levels. In effect, when a sample reaches the laboratory for lamotrigine level analysis, analysis will only begin once a certain number of similar samples are gathered, which ultimately generates delay. To combat non-compliancy to blood tests, we could contemplate implementing a structured follow-up system (phone calls or emails) for patients from whom we do not receive ASM levels. As for logistical causes for which results may be lost before reaching our clinic, we should aim to investigate and reformat the ASM level blood test delivery process. This reformatting could also help in diminishing blood test reception delays.

Telephone Follow-Ups

Currently, there is no consensus as to what the best medical practices are for how an epilepsy clinic should follow their pregnant patients. Our clinic functions mainly through telephone follow-ups for pregnant patients, as reflected in the results of our audit, for patient convenience. Though our median number of telephone follow-ups was two, the actual median was probably higher because telephone follow-ups aimed at informing patients of their blood test results without making medication adjustments were not noted in the patient files. Most pregnancies occurred without the patient having any in-person interactions. Our study does not provide sufficient data to conclude on the optimal timing or method for pregnancy care in WWE; more research should ideally be done to address this topic.

Pre-pregnancy Care

Issues pertaining to the pre-pregnancy care offered to WWE include pregnancy planning, specialized counseling, contraception use, and folic acid use. For WWE, pregnancy is a complicated experience that requires expert counseling advice. Nevertheless, unplanned, unintended pregnancies are common. An American survey of more than 500 WWE between 2009 and 2014 showed that 55% of pregnancies in this population were unintended.[16] The unintended pregnancy rate for Canadian women (not specifically having epilepsy) was 27% in 2006, and this rate remained stable in 2016.[17,18] Here, we provide the first unintended pregnancy rate specific to Canadian WWE (28%), grossly resembling the rate for Canadian women in general. Our unintended pregnancy rate in WWE may differ from the 55% reported by the aforementioned American survey due to demographical differences (Canada versus U.S.) and due to discrepancies in study design (e.g., cross-sectional versus longitudinal). Our clinic managed to provide specialized pre-pregnancy/early pregnancy counseling in 62% of cases, a number that should be improved given that 72% of pregnancies were reportedly intended. As for contraception, its usage can be complex in WWE due to interactions between hepatic enzyme-inducing ASMs (e.g. carbamazepine, oxcarbazepine, and phenytoin) and hormonal contraceptives.[12] Although our findings show that 19% of pregnancies occurred in women who were on contraception, two cases were distinctly problematic in that they featured a combination of enzyme-inducing ASM and hormonal contraception. One woman was taking phenytoin when her vaginal ring failed her, whereas the other woman was taking oxcarbazepine

https://doi.org/10.1017/cjn.2021.190 Published online by Cambridge University Press

when her oral contraceptive pill failed her. Particular attention should be dedicated to WWE on enzyme-inducing ASMs to ensure such events do not reoccur. On a final note, our findings show that 76% of pregnancies occurred in patients who were on folic acid, a rate which is higher than the 43.6% that has been reported in the past for WWE.[16] We should nevertheless attempt to increase folic acid usage by enhancing counseling efforts in WWE of childbearing age.

Seizure Control

Factors that may affect seizure control during pregnancy are under investigation. Latest guidelines suggest that pre-pregnancy seizure control is the chief predictor of seizure control during pregnancy, as demonstrated by numerous studies.[4,19–21] However, other predictors for seizure control have been suggested. A 2013 European study showed that women with focal rather than generalized epilepsy and on lamotrigine monotherapy rather than other ASM monotherapies were less likely to remain seizure-free during pregnancy.[22] A 2013 Japanese study showed that seizure frequency was lower when pregnancy was planned rather than unplanned.[23] A 2020 Spanish study demonstrated that seizure occurrence during pregnancy was associated with poor pre-pregnancy seizure control, ASM polytherapy, and untreated epilepsy.[21] In our study, we investigated factors associated with the occurrence of disabling seizures during pregnancy, whereas other studies mostly studied seizures independently of how disabling they were. Our analyses showed that most pregnancy characteristics did not differ according to disabling seizure occurrence. Nevertheless, a younger patient age was associated with disabling seizure occurrence during pregnancy, a finding that may be incidental or reflect how women may attain better seizure control the longer they have been under our care. A higher number of ASMs used during pregnancy and disabling seizure occurrence in the pre-pregnancy year were also associated with disabling seizure occurrence during pregnancy, findings which are consistent with the literature.[4,19–21] Interestingly, lamotrigine usage was associated with disabling seizure occurrence during pregnancy, and this association held true for lamotrigine used in polytherapy but not as monotherapy. Many factors probably played a role in this finding: (a) lamotrigine levels are known to greatly fluctuate during pregnancy; (b) our clinic only receives lamotrigine levels around two weeks after blood sampling; (c) there is a certain non-adherence to blood tests in our studied population (30%); (d) usage of lamotrigine in polytherapy may signal a more complicated underlying epilepsy; and e) our sample size may have been too small to demonstrate that lamotrigine monotherapy was also associated with disabling seizure occurrence.[12,13] Our practice should reflect our knowledge of potential risk factors for disabling seizure occurrence during pregnancy. As such, perhaps a closer follow-up should be envisaged for pregnant WWE who have had disabling seizures in the pre-pregnancy year and/or who are on ASM polytherapy, particularly if this polytherapy includes lamotrigine. There is a need for larger scale studies to confirm/infirm which factors actually predict disabling seizure occurrence during pregnancy, with special focus on the role of lamotrigine polytherapy in pregnancy seizure control.

Congenital Malformations and Neurodevelopmental Disorders

Finally, only one congenital malformation – a thyroglossal duct cyst – was reported in the child of a patient who took carbamazepine during pregnancy. Thyroglossal duct cysts are not known to be associated with carbamazepine usage.[10] Our audit's congenital malformation rate was 2%, which differs only slightly from the 1.7% rate in the North American Antiepileptic Drug Pregnancy Registry's external controls.[9] One child of a patient who took carbamazepine during pregnancy developed ASD. Data are sparse and inconclusive concerning the association between in utero carbamazepine exposure and neurodevelopmental disorders.[24] Our audit's ASD rate was 2%, which resembles the general prevalence of ASD of 1.85% in 8-year-old children.[25] A more detailed discussion of the relationship between ASM usage, congenital malformations, and neurodevelopmental disorders is beyond the scope of this study.

Limitations

Our study featured certain limitations. Firstly, although patients were recruited prospectively over the course of 18 years, our sample size was still limited, which in turn affected the power at which comparative analyses could be performed. This limited sample size may be due to the nature of the recruiting epileptologist's practice (e.g., in an academic tertiary care setting, cases may have been more complex, and patients may therefore have been less likely to achieve pregnancy). Secondly, although we conducted a systematic collection of data by reviewing patient files and by afterwards interviewing patients, some data were still missing and were treated with pairwise deletion. Thirdly, we could not account for ASM combinations in our audit. Fourthly, inherent biases may accompany the retrospective nature of this study. Fifthly, the generalizability of our findings may be difficult since these reflect the practice of an epileptologist in an academic tertiary care centre. Sixthly, our manner of determining if a patient's child presented ASD was by questioning the mother through the telephone, with no crosscheck with medical records. Finally, the sheer number of univariate comparisons that were performed may cloud the significance of some of our findings.

Conclusion

To our knowledge, this study represents the first Canadian audit of care for pregnant WWE. Our audit provides a descriptive synthesis of relevant pregnancy characteristics in a population of WWE followed in a specialized epilepsy clinic. Our exploratory analyses provide additional information on which factors may contribute to disabling seizure occurrence during pregnancy. Further research must be conducted to elucidate risk factors for seizure occurrence during pregnancy so that patients with greater risk of disabling events may be followed accordingly.

Acknowledgements

DKN holds a Canada Research Chair in Epilepsy.

https://doi.org/10.1017/cjn.2021.190 Published online by Cambridge University Press

Conflicts of Interest

DKN holds a Canada Research Chair in Epilepsy. The remaining authors have no conflicts of interest to declare.

Statement of Authorship

JL: role in study design, data collection, data analysis, drafting, and manuscript revision.

DHT: role in study design, study coordination, and manuscript revision.

DKN: role in study design, data collection, study coordination, and manuscript revision.

Supplementary Material

To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2021.190.

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