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Antiepileptic drug use during pregnancy: Perinatal outcomes

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ABSTRACT

Purpose: This study was undertaken to (1) measure the frequency of AED monotherapy or polytherapy during pregnancy and AED discontinuation prior to pregnancy in a cohort of women with treated epilepsy; and (2) describe the frequency of major congenital malformations according to maternal use of AED during pregnancy.
Methods: A cohort of epileptic pregnant women was identified within the Quebec Pregnancy Registry and was divided into three groups based on maternal AED use during pregnancy: AED monotherapy, AED polytherapy and no AED use.
Results: Of the 349 pregnancies meeting eligibility criteria, 79.6% were exposed to AED monotherapy and 5.8% to polytherapy during pregnancy; 14.6% discontinued AED prior to pregnancy. The most commonly used AEDs were carbamazepine (29.9%) and valproic acid (19.7%); the most common AED polytherapy combination was carbamazepine combined with clobazam (2.5%). Of 111 deliveries in the group of women on monotherapy during pregnancy, 9.9% ($n = 11$) were born with major congenital malformations; in the group of women treated with polytherapy, 19.0% ($n = 8$ over 42) of babies had major congenital malformations compared to 20.0% in women who discontinued AEDs prior to pregnancy.
Conclusion: This study demonstrates that the majority of women suffering from epilepsy were treated with monotherapy rather than polytherapy during pregnancy. While most used other agents, an important number of women continued to use valproate in pregnancy despite the long standing evidence of its teratogenicity and increasing evidence of its neuro-toxicity to the fetus.

1. Introduction

Prevalence of epilepsy in pregnant women has been estimated at 0.3–0.7%.[1,2] Despite the rarity of this neurologic disorder, epilepsy presents important clinical challenges during pregnancy. In fact, infants of women with epilepsy are known to be at increased risk of congenital malformations believed to be due mainly to the teratogenic effect of anti-epileptic drugs (AEDs) rather than the underlying epileptic disorder itself.[2,3] It is increasingly believed that the disease itself plays a minor role in the etiology of congenital malformations[3–6] though it may have a greater role in the occurrence of other adverse perinatal outcomes.[1]

The challenge in the treatment of women with epilepsy prior to and during pregnancy is to balance between the benefits to the mother from maintaining an effective treatment regimen and the risks: to the fetus from medications with recognized teratogenic potential, or to the mother from a sub-optimal management of epilepsy.[7] Monotherapy has been shown to be safer for the fetus than polytherapy as it has been shown to be associated with a lower risk of congenital malformations.[8–11] Several studies have also suggested that older antiepileptic drugs are more likely to cause congenital malformations than the newer ones.[12–15] In particular, valproate has been shown to hold the greatest teratogenic potential.[4,6,11,16–18] However, data comparing the safety of newer antiepileptic drugs use versus the older ones are still missing. Although these data are missing, the use of second generation AEDs are gaining popularity in a number of countries, and the need for studies investigating the factors behind AEDs prescription during pregnancy as well as their influence on pregnancy outcomes have been recently raised.[19]

The aim of our study was therefore to estimate the frequency of AED monotherapy or polytherapy during pregnancy and AED discontinuation prior to pregnancy in a cohort of women with previously diagnosed and treated epilepsy. We also described the characteristics of women according to AED use. In addition, we reported the frequency of major congenital malformations and other adverse pregnancy outcomes in infants born to women with epilepsy according to maternal use of AED during pregnancy.

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2. Methods

2.1. Study setting

This study was conducted within the Quebec Pregnancy Registry. This registry was built with the linkage of three administrative databases: the *Régie de l'Assurance Maladie du Québec* (RAMQ), Med-Echo, and the *Institut de la Statistique du Québec* (ISQ). The RAMQ database provides prospectively collected information on medical services dispensed to all residents of Quebec and on prescription filling information for residents insured by the Quebec Public Prescription Drug Insurance Plan. This database provides data on filled prescriptions, physician-based diagnoses (according to the *International Classification of Diseases*, ninth revision, ICD-9), physician and emergency department visits, medical procedures and hospitalizations, and patient and health care provider characteristics. Although RAMQ covers all Quebec's residents with respect to visits to the physician and the inherent fees, hospitalizations, and procedures, not all residents are covered by its Public Prescription Drug Insurance Plan. The RAMQ drug plan covers individuals who are 65 years and older, recipients of social assistance, and workers and their families (adherents) who have no access to a private drug insurance plan through their employers. These individuals account for approximately 42% of the overall Quebec population and 30% of pregnant women.[20] The Med-Echo database is a provincial database which records acute care hospitalization data for all Quebec residents; it also records gestational age (defined from the first day of the last menstrual period to the end of pregnancy, confirmed by ultrasound) for planned and spontaneous abortions, and deliveries. The ISQ administers the *Fichier des événements démographiques* that provides data on all births and deaths in Quebec, including birth weight and gestational age. All data in the three administrative databases are collected routinely and prospectively as part of the universal health care system in Quebec. Linkage between databases was done using subjects' unique personal identifier (*Numéro d'assurance maladie* (NAM)). The Quebec Pregnancy Registry is a registry including all pregnancies occurred in Quebec between the beginning of 1998 and the end of 2003. Pregnancies are identified in RAMQ database by a prenatal visit, and ICD-9 diagnostic or a procedure code related to pregnancy; and in Med-Echo by a procedure code related to a pregnancy including a planned or spontaneous abortion or a delivery (liveborn or stillbirth). Women are followed from the beginning of pregnancy (date of entry in the Registry), which is defined as the first day of the last menstrual period confirmed by ultrasound, until the end of pregnancy (planned or spontaneous abortion, or delivery, whichever comes first). The Quebec Pregnancy Registry has been used in the past for epidemiological research leading to scientific articles published in peer-reviewed medical journals.[20–23] Data recorded in the RAMQ medication database and in the Med-Echo database have been formally compared to data in patients' charts and physician reviews and found to be comprehensive and valid.[24] Physician-based medical diagnoses and data recorded in the ISQ databases have been compared to information present in patients' charts and have been found to be valid and accurate.[25,26] Studies using pregnant women insured by the RAMQ for their medications have been shown to generate valid risk estimates.[26–28]

2.2. Study population

Within the Quebec Pregnancy Registry, we selected all women who were between 15 and 45 years of age on the first day of gestation (date of entry in the Registry) and were continuously insured by the RAMQ drug plan for at least 12 months prior to and during pregnancy. The end of pregnancy was defined as the calendar date of a planned or spontaneous abortion, or a delivery. If a woman had more than one pregnancy between 01/01/1998 and 12/31/2003, the first pregnancy meeting eligibility criteria was included for analysis.

2.3. Pregnant epileptic women cohort

The cohort of pregnant epileptic women accounted for all women within the study population who had filled at least one prescription for an AED in the 12 months prior to the first day of gestation and were diagnosed with epilepsy (ICD-9 codes: 3450.x) in the 60 days preceding or following the dispensation date.

2.4. Exposure frequency of antiepileptic drug use during pregnancy

We stratified the pregnant epileptic women cohort into 3 groups based on their AED exposure during pregnancy: (1) no AED, (2) AED monotherapy and (3) AED polytherapy (women who filled one prescription for at least two different AEDs). To be considered as being exposed to AED, women had to have filled at least 1 prescription for an AED during pregnancy (defined as carbamazepine, clobazam, clonazapam, ethosuximide, gabapentine, lamotrigine, phenobarbital, phenytoin, primidone, topiramate, valproic acid or vigabatrin). The frequency of AED use before, during, and after pregnancy was calculated. The frequency of AED use during the 12-month period before pregnancy was calculated by dividing the number of women exposed to AED in the 12 months prior to pregnancy by the total number of women in the study population. Similarly, frequency of use during the whole pregnancy – as well as during the first (0–14 weeks of gestation), the second (>14–26 weeks of gestation) and the third trimester (>26 weeks of gestation) of pregnancy – was calculated. The number of women exposed to AED in each period was divided by the number of women in the study population at that time (depending on the outcome of the pregnancy, some women were counted in the denominator only in the first or second trimester). The frequencies of patients exposed to specific AEDs in monotherapy and polytherapy were calculated for the total duration of pregnancy and for each trimester separately.

2.5. Demographic and health care resource utilization

The following covariates were measured for the 3 AED exposure groups: (1) on the first day of gestation [maternal age, maternal place of residence (urban vs. rural), and maternal RAMQ drug plan status (adherent vs. welfare recipient)], (2) in the 12 months prior to pregnancy [number of different prescribers, number of different medication used other than AED, planned or spontaneous abortion (yes/no), number of physician visits, number of neurologist visits, psychiatrist visits (yes/no), emergency department visits or hospitalization (yes/no), hypertension (ICD-9: 401.0–405.9, 362.1, 416.0, 437.2, 796.2) or use of antihypertensive drugs (yes/no), and diabetes (ICD-9: 250.0–250.9, 271.4, 790.2) or use of oral hypoglycemic medications or insulin (yes/no)].

2.6. Pregnancy outcomes

We obtained information on whether each pregnancy in the cohort of pregnant epileptic women ended in a planned or spontaneous abortion or a delivery (live birth or stillbirth). For each live birth, we obtained information on whether the baby was diagnosed with at least one major congenital malformation (ICD-9, 740.0–759.9, excluding the following minor malformations: 743.6, 744.1, 744.4, 744.6, 747.0, 747.5, 750.0, 752.4, 752.5, 754.6, 755.0, 755.1, 757.2–757.6, 757.8, 757.9 and 758.4) anytime during the first year of life. We also measured for each live birth, the status of

small-for-gestational-age (SGA), low birth weight (LBW) and preterm gestation. A newborn was consider as SGA if his weight adjusted for gestational age and gender was <10th percentile, according to the Canadian gender-specific reference curves.[29] The criterion for LBW was a weight <2500 g, and preterm birth was defined as a birth occurring at gestational age <37 weeks.

2.7. Statistical analysis

To describe the study population in terms of AED exposure during pregnancy, we presented means and proportions for continuous and dichotomous variables, respectively. We estimated crude odds ratios (ORs) for the associations between AED exposure status and the risk of major congenital malformations, SGA, LBW, and prematurity, separately, with 95% confidence intervals (95% CI) using logistic regression models. All statistical analyses were performed using the SAS software version 9.1 (SAS Institute).

2.8. Ethics approval

This research project was approved by the Sainte-Justine's Hospital Ethic's Committee and the linkage between administrative databases was authorized by the 'Commission d'Accès à l'Information du Québec'.

3. Results

Within the Quebec Pregnancy Registry, 109 344 pregnant women met the inclusion criteria, and thus formed the study population. The frequency of AED exposure in this cohort during the 12 months prior to pregnancy was 0.32% (95%CI: 0.29%, 0.35%) (Table 1). Frequencies of AED exposure declined significantly during the first trimester compared to 12 months prior to pregnancy (0.27% vs. 0.32%, $p = 0.04$), and continued to decrease during the second (0.22%, $p < 0.001$), and third trimesters (0.23%, $p = 0.001$) (Table 1). The number of pregnant women in the study population dropped to 90 111 during the second trimester and 64 171 in the third trimester due to planned and spontaneous abortions, or preterm deliveries (Table 1).

Table 1
Frequency of AED utilization prior to and during pregnancy.

Period considered	Number of AED users	Total number of pregnant women[a]	Percent (95% CI)
12 months prior pregnancy	349	109 344	0.32% (0.29–0.35%)
Overall pregnancy	307	109 344	0.28% (0.25–0.31%)
1st trimester (≤14 weeks)	297	109 344	0.27% (0.24–0.30%)
2nd trimester (>14 and ≤26 weeks)	202	90 111	0.22% (0.19–0.26%)
3rd trimester (>26 weeks)	146	64 171	0.23% (0.19–0.26%)

[a] At the beginning of the period considered.

Table 2
AED exposure during pregnancy with respect of prior AED exposure.

AED exposure prior to pregnancy	AED exposure during pregnancy		
	Monotherapy	Polytherapy	Non exposed
Monotherapy (%)	191 (79.6%)	14 (5.8%)	35 (14.6%)
Polytherapy (%)	26 (23.9%)	76 (69.7%)	7 (6.4%)

The cohort of pregnant epileptic women included 349 women exposed to AED in the 12 months prior to pregnancy (Table 2). The majority of these women (79.6%) received AED monotherapy during pregnancy; 5.8% received polytherapy during pregnancy, and 14.6% were not exposed to AED at any time during gestation (Table 2). Over the course of pregnancy we observed a reduction of 5.5% in the number of women exposed to more than one AED.

Characteristics of the cohort of pregnant epileptic women for the three groups of AED exposure status during pregnancy are presented in Table 3. Women in each AED exposure group were similar with respect to age and area of residence (rural vs. urban) on the first day of gestation, and for all variables related to health care services use in the 12 months prior to pregnancy except that

Table 3
Characteristics of epileptic women with respect to AED use during pregnancy.

Variables	Epileptic women ($N = 349$)			p-Value
	Non use ($N = 42$)	Monotherapy ($N = 217$)	Polytherapy ($N = 90$)	
On the first day of gestation				
Maternal age, years (mean ± SD)	27.5 ± 6.4	27.2 ± 6.0	27.6 ± 6.4	0.25
Rural dwellers (n (%))	7 (16.7)	48 (22.1)	18 (20.0)	0.71
Welfare recipients (n (%))	22 (52.4)	91 (41.9)	64 (71.1)	<0.001
In the 12 months prior to first day of gestation				
Number of different prescribers (n (%))				
2 or less	14 (33.3)	23 (25.6)	73 (33.6)	
3 or more	28 (66.7)	67 (74.4)	144 (66.4)	0.37
Number of different medications used other than AED (n (%))				
2 or less	16 (38.1)	67 (30.9)	27 (30.0)	
3–5	5 (11.9)	44 (20.3)	14 (15.6)	
More than 5	21 (50.0)	106 (48.8)	49 (54.4)	0.58
Number of physician visits (n (%))				
2 or less	3 (7.1)	17 (7.8)	3 (3.3)	
3–5	5 (11.9)	39 (18.0)	11 (12.2)	
More than 5	34 (81.0)	161 (74.2)	76 (84.4)	0.32
Psychiatrist visits (n (%))	5 (11.9)	19 (8.8)	12 (13.3)	0.46
Neurologist visits (n (%))				
0	10 (23.8)	66 (30.4)	15 (16.7)	
1	15 (35.7)	84 (38.7)	23 (25.6)	
2 or more	17 (40.5)	67 (30.9)	52 (57.8)	<0.001
Emergency department				
Visits/hospitalization (n (%))	10 (23.8)	48 (22.2)	24 (26.7)	0.69
Abortion/miscarriage (n (%))	1 (2.4)	6 (2.8)	3 (3.3)	0.94
Hypertension (n (%))	0 (0.0)	5 (2.3)	2 (2.2)	0.51
Diabetes (n (%))	0 (0.0)	2 (0.9)	1 (1.1)	0.57

Table 4
Pregnancy outcomes among population of epileptic women.

	Non use ($N=42$)	Monotherapy ($N=217$)	Polytherapy ($N=90$)	p-Value[a]
Outcomes				
Abortions (n (%))	19 (45.2)	88 (40.5)	40 (44.4)	
Miscarriage (n (%))	0 (0.0)	6 (2.8)	4 (4.4)	
Delivery (n (%))	23 (54.8)	123 (56.7)	46 (51.1)	0.33
	Non use ($N=21$)	Monotherapy ($N=123$)	Polytherapy ($N=42$)	p-Value[a]
Number of deliveries at ISQ				
Stillbirth (n (%))	1 (2.4)	0 (0.0)	1 (2.4)	
Live birth (n (%))	20 (95.0)	123 (100.0)	41 (97.6)	0.10
	Non use ($N=20$)	Monotherapy ($N=111$)	Polytherapy ($N=42$)	p-Value[a]
Number of babies				
Major congenital malformation (n (%))	4 (20.0)	11 (9.9)	8 (19.0)	0.22
Low birth weight[b] (n (%))	2 (10.5)	9 (8.2)	3 (7.1)	0.91
Prematurity[b] (<37 weeks) (n (%))	3 (15.8)	11 (10.0)	4 (9.5)	0.73
SGA[b] (<10th percentile) (n (%))	1 (5.3)	20 (18.2)	5 (11.9)	0.28

[a] Kruskal–Wallis test.
[b] Based on 171 babies (19, 110 and 42 respectively).

women on AED polytherapy had more neurologist visits than the others. In addition, women exposed to AED polytherapy regimens were more likely to be welfare recipients.

During pregnancy, the three most prevalent AEDs used were carbamazepine (29.9%), valproic acid (19.7%) and phenytoin (11.5%). The most common drug combinations of AEDs used in polytherapy included carbamazepine combined with clobazam (2.5%), phenytoin (1.6%) and valproic acid (1.6%).

Of the 349 pregnant epileptic women, 192 (55.0%) pregnancies ended with a delivery; 147 (42.1%) resulted in a planned abortion and 10 (2.9%) in a spontaneous abortion. The linkage with the ISQ database was possible for 173 babies (90% of all deliveries). Table 4 presents the distribution of the number of babies with major congenital malformations diagnosed in the first year of life, SGA, LBW, and prematurity for the three AED exposure groups. The proportion of babies born with major congenital malformations was higher in the group of women with epilepsy who did not receive AED treatment during pregnancy (20%) and in the group of epileptic women exposed to more than one AED during pregnancy (19%) compared to the women exposed to only one type of AED during gestation (9.9%). LBW as well as prematurity were more frequent among epileptic women who were not exposed to AED during their pregnancy compared to women exposed to AED. In contrast, the proportion of SGA was higher among epileptic women exposed to AED than among non-exposed epileptic women. None of the differences observed were statistically significant (Table 4).

4. Discussion

Using a large population-based pregnancy registry, we estimated that 0.28% of pregnant women use AED during pregnancy. This is in line with the published estimates (0.3–0.5%) of the prevalence of epilepsy in pregnant women.[1,2] The majority of women with epilepsy in our study received monotherapy during pregnancy suggesting that there is recognition of the importance to both mother and fetus of continued control of the symptoms of epilepsy during gestation. Prevalence in AED monotherapy differs largely between regions and lies between 3.5% and 75% as recently shown by the EURAP Study Group.[19] Indeed only 12% of women with treated epilepsy prior to pregnancy received no AEDs during gestation. This, in combination with the observed decline in the use of polytherapy in favour of monotherapy over the course of pregnancy, reflects current understanding that on balance, and when possible, monotherapy during pregnancy may be safest for both mother and fetus. We observed that women who used an AED polytherapy regimen during pregnancy were more likely to be welfare recipients or to attend neurologist visits more frequently in the 12-month period prior to the first day of gestation than those on AED monotherapy or no therapy. These characteristics may be indicators of more severe illness among women using polytherapy during pregnancy.

In this study, the most commonly used AED, whether in monotherapy or polytherapy, was carbamazapine. This is consistent with findings of the EURAP study which showed that in the majority of countries (over 38 countries in total) carbamazepine is the most commonly AED to be used during pregnancy.[19] Indeed, almost two-thirds of the AEDs used in pregnancy were the so-called older generation AEDs. Carabamazapine has been shown to be a comparatively safer choice for the control of epileptic seizures during pregnancy.[4,6,17,18,30] Valproate, on the other hand, has long been shown to hold teratogenic potential if used during the first trimester of pregnancy. More recently it has been shown to be fetotoxic, posing overall delayed early development[31] and neurodevelopmental risks throughout pregnancy.[16] That valproate was the second most commonly used AED in monotherapy during pregnancy and that 20% of pregnancies that proceeded under monotherapy were exposed to valproate is a result that is of some concern and one that warrants further study. However, studies showed that when seizures are well controlled with valproic acid, it is therefore difficult to switch to another antiepileptic drug before or during pregnancy. This could explain why women continue to be treated with valproate during pregnancy.[32,33] We did not assess whether other AEDs were tried and evaluated before pregnancy, nor did we assess whether a dose reduction prior to pregnancy had been implemented.

In this study we defined women with treated epilepsy according to strict criteria: having filled a prescription for an AED within 60 days of a diagnostic code for epilepsy in the year prior to pregnancy. Both criteria had to be fulfilled in order to meet eligibility requirements for the study. This ensured that the study was conducted among women with documented and treated epilepsy. It is nevertheless possible that some women with long standing treated epilepsy could have been excluded if they continued on their AEDs with no physician visit within 60 days of having filled a prescription. We expect that the number of women excluded in this way would be low, and have no reason to believe that their pregnancy experiences or outcomes would be different from the women included in the study. Our choice resulted in a specific cohort of epileptic women who became pregnant.

We also reported on several perinatal outcomes according to maternal AED exposure. The number of women in each group was small, leading to a lack of statistical power needed for robust interpretation of these results. Proportion of major congenital malformations was higher among women who were on polytherapy compared to women on monotherapy which is consistent with previous findings.[11] However, this difference was not statistically significant. Nevertheless, it was of interest that in this study women with epilepsy who used no AEDs during pregnancy and those who used polytherapy during pregnancy delivered a similar proportion of infants born with major congenital malformations, nearly double of those who used monotherapy. In fact, 25–30% of women with epilepsy experience an increase in their seizure activity during pregnancy.[34] Therefore, the higher risk of congenital malformation in the untreated group compared to the group treated with monotherapy could be explained by the maternal seizure disorder itself. In fact, the rate of malformation is comparable between the untreated group and the group treated with polytherapy which could suggest that the best way to control the disease and protect the baby would be, similarly to what was reported in the literature, having a monotherapy treatment rather than not treating or treating with two or more antiepileptic drugs.[35] The frequency of planned abortions was higher in the study (42%) compared to the planned abortion prevalence among non-epileptic women of the overall Quebec Pregnancy Registry (36.2%) likely due to the particular concerns with pregnancy in epileptic women. Similar proportions of pregnancies were terminated by planned abortions in the three AED exposure categories. On the other hand a higher proportion of babies were born SGA following maternal monotherapy during pregnancy than under polytherapy or no AED use during pregnancy.

The strengths of our study include its large sample size, accurate information on filled medications without reliance on maternal recall, and physician-based diagnostics or procedures related to adverse pregnancy outcomes that are prospectively and routinely collected limiting the potential for detection bias. Gestational age, previously validated,[26] was obtained from hospital charts, which enabled us to calculate exact timing of AED exposure during pregnancy. Finally, diagnoses of major congenital malformations have previously been validated.[36]

Limitations of this study include the use of exposure data based on prescription fillings, which might not necessarily reflect actual intake. However, we hypothesize that women who filled a prescription for an AED took at least one dose since within the Quebec drug plan they need to pay in part for their medications. Therefore, given the design of our study, this would not invalidate our findings. Also, we were not able to take into account the type and severity of epilepsy, not the dosage of the different AEDs used in our cohort. In addition, since we are using administrative databases, information on potential confounding variables such as smoking and maternal obesity was not available. However, given that we have performed multivariate analyses among pregnant women with epilepsy, our comparison groups tend to be similar in terms of lifestyles, thus decreasing the likelihood of such a bias. Also, we feel confident that although our sample consisted of women from a relatively disadvantaged socioeconomic background, we do not think that this would bias our results. In fact, socioeconomic status was found to be an effective modifier in the Quebec Pregnancy Registry but not a confounder.[27] Moreover, although previous studies associated incidence of epilepsy with age and socioeconomic status,[37,38] to our knowledge, no studies have shown association between socio-economic status and severity of epilepsy. Therefore we do not believe that being covered RAMQ drug plan is associated with the degree of severity of the disease. Finally, the fact that our study population covers only 30% of pregnant women in Quebec does not affect the validity of our findings though it might influence generalisability.

This study demonstrates that the majority of women with epilepsy were treated with monotherapy rather than polytherapy during pregnancy. While most used other agents, an important number continued to use valproate in pregnancy in the face of long standing evidence of its teratogenicity and increasing evidence of its feto-toxicity. This finding raises a concern and a need of future studies investigating the reasons behind valproate use in pregnancy and other possible alternative treatments.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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