HIGH LIGHT

CME

Seizure control and treatment in pregnancy

Observations from the EURAP Epilepsy Pregnancy Registry

The EURAP Study Group*

Abstract—*Objective:* To analyze seizure control and treatment in pregnant women with epilepsy. *Methods:* Seizure control and treatment were recorded prospectively in 1,956 pregnancies of 1,882 women with epilepsy participating in EURAP, an international antiepileptic drugs (AEDs) and pregnancy registry. *Results:* Of all cases, 58.3% were seizure-free throughout pregnancy. Occurrence of any seizures was associated with localization-related epilepsy (OR: 2.5; 1.7 to 3.9) and polytherapy (OR: 9.0; 5.6 to 14.8) and for tonic-clonic seizures, with oxcarbazepine monotherapy (OR: 5.4; 1.6 to 17.1). Using first trimester as reference, seizure control remained unchanged throughout pregnancy in 63.6%, 92.7% of whom were seizure-free during the entire pregnancy. For those with a change in seizure frequency, 17.3% had an increase and 15.9% a decrease. Seizures occurred during delivery in 60 pregnancies (3.5%), more commonly in women with seizures during pregnancy (OR: 4.8; 2.3 to 10.0). There were 36 cases of status epilepticus (12 convulsive), which resulted in stillbirth in one case but no cases of miscarriage or maternal mortality. AED treatment remained unchanged in 62.7% of the pregnancies. The number or dosage of AEDs were more often increased in pregnancies with seizures (OR: 3.6; 2.8 to 4.7) and with monotherapy with lamotrigine (OR: 3.8; 2.1 to 6.9) or oxcarbazepine (OR: 3.7; 1.1 to 12.9). *Conclusions:* The majority of patients with epilepsy maintain seizure control during pregnancy. The apparently higher risk of seizures among women treated with oxcarbazepine and the more frequent increases in drug load in the oxcarbazepine and lamotrigine cohorts prompts further studies on relationships with pharmacokinetic changes. Risks associated with status epilepticus appear to be lower than previously reported.

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The treatment of epilepsy during pregnancy is particularly challenging in that the potential adverse effects of antiepileptic drugs (AEDs) on the fetus need to be balanced against the maternal and fetal risks associated with uncontrolled seizures. The prevailing treatment strategy is to use one AED appropriate to control seizures, particularly tonic-clonic seizures, at the lowest effective dosage.[1] While great efforts are made to determine and compare the teratogenic potential of different AEDs,[2-5] few recent studies have assessed potential changes in seizure control during pregnancy. Reports detailing the impact of pregnancy on seizure control were published as early as the 19th century. In a frequently quoted work,[6] 2,065 pregnancies in reports published until 1980 were reviewed and it was concluded that seizure frequency increased in 24%, decreased in 23%, and remained unchanged in the remaining 53% of cases. Most of these early studies were on selected patients from epilepsy centers and often retrospective in design. Subsequent population-based studies have confirmed that 54 to 67% of patients have unchanged seizure control whereas 15 to 32% deteriorate during pregnancy.[7-10] A major limitation in all studies is a small sample size, with the largest prospective reports having no more than 110 to 154 patients.[7,11-14] Information on seizure control during pregnancy based on large studies and from more recent years is thus lacking.

In this article, we report seizure control and treatment strategies during pregnancy in a cohort of almost 2,000 patients with epilepsy from EURAP, a

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prospective international antiepileptic drugs and pregnancy registry. The primary objective of EURAP is to compare the teratogenic potential of different AEDs. However, the occurrence of seizures and status epilepticus during pregnancy is also recorded prospectively, allowing us to analyze seizure control and treatment changes in the setting of a large prospective observational study.

Methods. *Inclusion criteria and study procedures.* EURAP was set up in 1999 as a collaboration between independent research groups in different countries.[2] It has gradually expanded to involve more than 300 collaborators from over 30 countries worldwide. Women taking AEDs for any indication at the time of conception are eligible for inclusion, subject to their willingness to provide informed consent. Only pregnancies registered within week 16 of gestation and before fetal outcome is known contribute to the prospective study. Information on patient demographics, underlying disease, family history of malformations, drug therapy, and a large set of other potential risk factors is obtained. Data on seizure frequency and the occurrence of status epilepticus are also recorded prospectively once each trimester. Data are collected online by the network of reporting physicians caring for the women during pregnancy. Collaborating physicians submit their reports to a national coordinator in their country for review and correction before the data are transferred to the EURAP central database in Milan, Italy. Missing data and inconsistencies are corrected through online interaction among the central registry, national coordinators, and reporting physicians. Ethics committees in the participating countries approved the study.

In this registry, seizures are classified by the reporting physician as either generalized tonic-clonic (convulsive seizures, including primarily and secondarily generalized tonic-clonic seizures) or other types of seizures (collectively labeled as nonconvulsive seizures in the present analysis) and quantified separately into one of six predefined frequency categories (no seizures, less than one seizure per month, monthly, weekly, more than weekly, and daily seizures). These categories reflect how data are collected with exact seizure counts or timing not being recorded as part of the EURAP protocol. The epilepsy or epileptic syndrome is classified according to the recommendations of the International League Against Epilepsy.[15] The occurrence of status epilepticus is recorded and classified as convulsive or nonconvulsive.

Enrollment of pregnant women started in three countries (Italy, Australia, and Sweden) in June 1999. At the end of January 2004, 1,882 women with epilepsy enrolled in 30 countries had been followed up prospectively throughout the entire pregnancy, for a total of 1,956 pregnancies. Seventy women had more than one pregnancy (two in 66 cases and three in 4 cases), 31 women had a twin pregnancy, and one a triplet. An additional 174 enrolled pregnancies were lost to follow-up and were thus excluded, as well as pregnancies from 29 patients taking AEDs for indications other than epilepsy. Enrollment by country is summarized in table 1.

Of the 1,956 evaluable pregnancies, 220 ended prematurely due to induced abortions (n = 57), spontaneous abortions (n = 133), or stillbirths (n = 30). Hence, prospective information on seizure control throughout a complete pregnancy was available for 1,736 pregnancies. The present analysis is mainly based on these pregnancies.

Statistical analysis. Results were expressed as frequency counts and means ± SD for all the variables.

Study endpoints included the following: occurrence of seizures, occurrence of convulsive seizures (expressed as present or absent), changes in AED load (number of AEDs or change in dosage), and changes in seizure frequency (expressed as increase or decrease, using seizure frequency in the first trimester as reference). The relationships of the above endpoints with two covariates (type of epilepsy and type of AED) were investigated by means of multivariable logistic regressions using JMP 5.2. Results are reported as OR with associated 95% CI. The covariates considered in the multivariate models were selected adopting the epidemiologic approach regardless of the univariate and subset selection findings. Monotherapy treatments accounting for fewer than 2% of all enrolled pregnancies were pooled together and called other monotherapies. A change in seizure frequency was defined as a switch from one frequency category to another. In the case of mixed seizure types, the greater change was recorded when one seizure type increased and the other decreased. Results were considered significant for p values < 0.05 (two sided); only significant results are reported in the text.

Table 1 *Countries contributing cases to the prospective assessment of seizure control during pregnancy listed by number of enrolled pregnancies*

	Enrolled pregnancies	
Country	n	(%)
Italy	489	(25)
Australia	266	(14)
Sweden	220	(11)
Norway	135	(7)
Denmark	124	(6)
Spain	99	(5)
Germany	94	(5)
The Netherlands	82	(4)
Austria	70	(4)
India	65	(3)
Turkey	67	(3)
Czech Republic	56	(3)
Other countries	189	(10)
Total	1,956	(100)

The following countries each contributed fewer than 2% of all enrolled pregnancies: Argentina, Belgium, Chile, Croatia, France, Georgia, Hungary, Israel, Japan, Lithuania, Macedonia, Poland, Scotland, Serbia-Montenegro, Slovakia, Slovenia, Switzerland, and United Kingdom.

Results. *Demographic data.* The mean duration of pregnancy at time of enrollment was 9.1 (±3.4) gestational weeks. Out of the 1,956 pregnancies, 111 (5.7%) were enrolled during the first 4 gestational weeks, 927 (47.4%) during the fifth through eighth week, 559 (28.6%) during the ninth through 12th, and 359 (18.4%) during weeks 13 to 16. The age at the last menstrual period of the women with prospective completed pregnancies ranged from 15.3 to 43.5 (mean 29.3 ± 4.9) years. The epilepsy syndrome was classified as generalized in 736 (42.4%), localization-related in 913 (52.6%), and undetermined in 66 (3.8%) pregnancies. Information on the epilepsy classification was missing in 21 (1.2%). AED polytherapy was used in 369 (21.3%) of the pregnancies, whereas the majority, 1,367 (78.7%), involved exposure to a single AED. Details of AED treatment are given in table 2.

Overall seizure control. Of all cases, 1,013 (58.3%) were seizure-free throughout pregnancy, whereas 723 (41.6%) had seizures, exclusively nonconvulsive in 406 cases (23.4%). The remaining 317 cases (18.3%) all had convulsive seizures but could also in addition have nonconvulsive seizures.

Seizure control during pregnancy by type of AED treatment is summarized in table 2.

Out of 736 pregnancies with generalized epilepsies, 503 (68.3%) were completely controlled compared to 451/913 (49.4%) of those with localization-related epilepsies.

Table 2 *Seizure control during pregnancy and delivery by type of pharmacologic treatment*

Treatment	Total treated		No seizures during pregnancy		Seizures during pregnancy and delivery (including cases with status epilepticus)			
					Generalized tonic-clonic seizures* (with or without other seizure types), n	Any other seizure type (those with tonic-clonic seizures* excluded), n	Total	
	n	(%)	n	(%)			n	(%)
Carbamazepine	498	(28.7)	327	(65.7)	68	103	171	(34.3)
Lamotrigine	238	(13.7)	135	(56.7)	42	61	103	(43.3)
Oxcarbazepine	41	(2.4)	17	(41.5)	14	10	24	(58.5)
Phenobarbital	117	(6.7)	83	(71.0)	20	14	34	(29.0)
Phenytoin	44	(2.5)	30	(68.2)	7	7	14	(31.8)
Valproic acid	345	(19.9)	263	(76.2)	34	48	82	(23.8)
Other monotherapies	84	(4.8)	44	(52.4)	11	29	40	(47.6)
Polytherapies	369	(21.3)	114	(30.9)	121	134	255	(69.1)
Total	1,736	(100)	1013	(58.3)	317	406	723	(41.7)

* Includes primary or secondary generalized tonic-clonic seizures.

Use of polytherapy was independently associated with an increased risk for occurrence of all seizures (OR 9.0; 5.6 to 14.8) and of convulsive seizures (4.2; 2.5 to 7.0). Likewise, localization-related epilepsy was associated with a greater risk for occurrence of all seizures (OR: 2.5; 1.7 to 3.9) and oxcarbazepine monotherapy with a greater risk for occurrence of convulsive seizures (OR: 5.4; 1.6 to 17.1).

Changes in seizure frequency. Seizure control during the second and third trimester was compared with that during the first trimester. Information on changes in seizure frequency was available for 1,718 pregnancies. Seizure frequency category did not change in 1,093/1,718 cases (63.6%), 1,013 (92.7%) of whom remained seizure-free during the entire pregnancy. Of the remaining 625 pregnancies, 273 (15.9%) improved in the second or third trimester (or both), and 298 (17.3%) deteriorated. In 54 pregnancies (3.1%), seizure frequency category changed in opposite directions in the second and the third trimesters.

Of the 298 pregnancies with increased seizure frequency, 86 showed higher frequency both in second and third trimesters than in the first, whereas in 210 cases deterioration of seizure control occurred in the second trimester (n = 100) or in third trimester (n = 110) only. In two additional cases seizure frequency deteriorated in the second trimester, whereas no information was available from the third trimester. At multivariate analysis, the risk of deterioration of seizures was higher in localization-related epilepsies (OR: 1.9; 1.1 to 3.5) and in pregnancies associated with polytherapy (OR: 3.9; 2.2 to 7.1) or oxcarbazepine monotherapy (OR: 4.6; 1.3 to 15.4). The proportion of patients improved was higher in localization-related epilepsies (OR: 2.2; 1.2 to 4.1) and pregnancies with polytherapy (OR: 6.3; 3.4 to 11.8) or the other monotherapies category (OR: 3.5; 1.2 to 9.9).

Seizures during delivery. Seizures occurred during delivery in 60 (3.5%) patients, including 28 cases of single primary or secondary generalized tonic-clonic seizures, 31 cases of other seizure types, and 1 case of convulsive status epilepticus. Fourteen of the 60 patients with seizures during delivery had been seizure-free throughout the entire pregnancy and 5 of the 29 patients with tonic-clonic seizures at delivery had only had nonconvulsive seizures during pregnancy. The only factor significantly associated with the risk of seizures during delivery was the occurrence of seizures earlier during pregnancy (OR: 4.8; 2.3 to 10.0).

Status epilepticus. Status epilepticus occurred in 36 of 1,956 (1.8%) pregnancies, and in 12 of these it was of convulsive type. Of the status episodes, 13 (3 convulsive) occurred in the first trimester, 11 (4 convulsive) in the second, and 13 (5 convulsive) in the third trimester (including one convulsive status at delivery and one convulsive status in a patient who had one convulsive status also in the second trimester). Details of AED treatment for patients who had status epilepticus through pregnancy or at delivery are given in table 3.

Nineteen of the pregnancies with status were in women with generalized epilepsy and 17 in women with localization-related epilepsy. No risk factors for status were identified. Nineteen patients had been seizure free during pregnancy until onset of status. Thirty were on monotherapy, with an AED distribution similar to that of the total cohort (see table 3). Prior to status, AEDs had been unchanged since conception in 18 cases, and dosage was decreased in only one woman. This particular case ended with a stillbirth in connection with the convulsive status episode. In the remaining 17 women, number or dosages of AEDs were increased, but no information is available on temporal relationship between treatment changes and occurrence of status. Thirty-four of the 36 pregnancies associated with status resulted in delivery of live born offspring. One patient with nonconvulsive status during the first trimester had a spontaneous abortion, but not in close proximity to the status episode. There were no maternal mortalities among the cases with status.

Table 3 *Status epilepticus during pregnancy by type of pharmacologic treatment*

Treatment	Total treated		Convulsive, n				Nonconvulsive, n			
	n	(%)	1st Trimester	2nd Trimester	3rd Trimester	Total	1st Trimester	2nd Trimester	3rd Trimester	Total
Carbamazepine	11	(36.6)	1	0	3*	4	3	1	3	7
Lamotrigine	4	(11.1)	0	1	0	1	2	1	0	3
Oxcarbazepine	2	(5.6)	1	1	0	2	0	0	0	0
Phenobarbital	3	(8.3)	0	0	0	0	1	1	1	3
Phenytoin	1	(2.8)	0	0	0	0	0	0	1	1
Valproic acid	7	(19.4)	1	1†	1	3	1	1	2	4
Other monotherapies	2	(5.5)	0	0	0	0	0	1	1	2
Polytherapies	6	(16.7)	0	1‡	1‡	2	3§	2	0	5
Total	36	(100)	3	4	5	12	10	7	8	25

* One convulsive status at delivery also.
† Stillbirth.
§ Spontaneous abortion in one of the cases although not in close temporal relationship to the episode of status epilepticus.
‡ Same pregnancy.

Spontaneous abortions and stillbirths. Among pregnancies ending in spontaneous abortion, 100 (74.1%) were completely seizure-free during pregnancy. The corresponding figure for pregnancies ending in stillbirth was 15 (50.0%). Only one of the stillbirths, and none of the spontaneous abortions, occurred in close proximity to a seizure or status epilepticus (see above).

Treatment changes. Treatment (type, number, or dosages of AEDs) remained unchanged in 1,089 pregnancies (62.7%). In 12 pregnancies, one AED was switched to another. The number of AEDs was reduced in 57 pregnancies and increased in 51. AED dosages were decreased in 137 and increased in 390 of the 1,616 pregnancies with constant AED type and number. Thus, the number of AEDs or their dosage were increased in about one quarter of the pregnancies (table 4). These changes occurred more often in the second than in the third trimester. Treatment was changed more often in pregnancies with seizures (383/715, 53.0%) than in those with complete seizure control (264/1013, 26.1%). The number of AEDs or their dosages were increased in 37.5% of uncontrolled pregnancies and decreased in 15.0%; the corresponding figures for seizure-free pregnancies were 17.1% and 8.6%. Among the 639 pregnancies with constant AED type and number and with seizures, AED dosage was reduced in 10.9%, increased in 35.8%, and unchanged in 53.2%.

Multivariate analysis confirmed that number or dosages of AEDs were more often increased or decreased in pregnancies with incomplete seizure control (OR: 3.6; 2.8 to 4.7 and 2.1; 1.5 to 3.0). Moreover, increase in AED load was independently associated with lamotrigine (OR: 3.8; 2.1 to 6.9) or oxcarbazepine (OR: 3.7; 1.1 to 12.9) monotherapy, whereas no association was found between decrease in AED load and a particular treatment, nor

Table 4 *Pregnancies in which drug load (dosage or number of antiepileptic drugs [AEDs]) was increased (vs previous trimester) in each AED group by trimester*

Treatment	Total no. of pregnancies assessed	Pregnancies with increase in AED load in 2nd trimester				Pregnancies with increase in AED load in 3rd trimester				Total no. of increases in AED load	
		Other AED added, n	Dose increased, n	AED added or dose increased		Other AED added, n	Dose increased, n	AED added or dose increased			
				n	(%)			n	(%)	n	(%)
Carbamazepine	498	4	47	51	(10.2)	5	30	35	(7.0)	86	(17.3)
Lamotrigine	238	7	69	76	(31.9)	4	30	34	(14.3)	110	(46.2)
Oxcarbazepine	41	2	13	15	(36.6)	0	3	3	(7.3)	18	(43.9)
Phenobarbital	117	3	15	18	(15.4)	1	13	14	(12.0)	32	(27.4)
Phenytoin	44	2	11	13	(29.5)	1	1	2	(4.5)	15	(34.1)
Valproic acid	345	2	36	38	(11.0)	3	24	27	(7.8)	65	(18.8)
Other monotherapies	84	4	8	12	(14.3)	2	5	7	(8.3)	19	(22.6)
Polytherapies	369	5	57	62	(16.8)	6	28	34	(9.2)	96	(26.0)
Total	1,736	29	256	285	(16.4)	22	134	156	(9.0)	441	(25.4)

AED = antiepileptic drug.

between any treatment change and type of epilepsy. These associations did not change when alteration in AED dosage was analyzed separate from change in number of AEDs. Multivariate analysis thus revealed that increase (OR: 2.5; 1.7 to 3.7) or decrease (OR: 3.3; 2.5 to 4.3) in AED dosage occurred more frequently in pregnancies with incomplete seizure control. Furthermore, increase in dosage of AEDs remained independently associated with lamotrigine (OR: 4.3; 2.3 to 7.8) and oxcarbazepine (OR: 4.1; 1.1 to 14.6) monotherapy.

Discussion. Published studies on the effect of pregnancy on seizure control are associated with a number of methodologic problems, one being the lack of a control group. In most cases, seizure control during pregnancy is compared with a pre-gestational baseline period in the same patient. However, while seizure control during pregnancy is often recorded prospectively, the pre-pregnancy baseline is evaluated retrospectively, which may result in a less accurate and potentially biased assessment. Furthermore, in many cases the management of epilepsy during pregnancy is likely to be different than during the nonpregnant state, in accordance with guidelines or local protocols. Finally, the vast majority of previous studies come from specialized epilepsy centers, which presumably manage highly selected patients, likely affecting how generalizable their results might be.

EURAP is not a population-based study. This report is based on data from more than 300 reporting physicians in 30 countries worldwide and the data generated from the study are therefore likely to be heterogeneous in many respects. Single epilepsy centers represent some countries, whereas in other countries, it is estimated that at least 20% of pregnant women with epilepsy on AEDs are enrolled. EURAP is a purely observational study and does not interfere with the clinical management of the patients. Therefore, management may vary among physicians, centers, and countries depending on local traditions, treatment programs, facilities, and other resources. It is, however, reasonable to assume that physicians choosing to take part in the EURAP network have a special interest and, perhaps, expertise in managing epilepsy in women of childbearing years. Although the data thus are likely to be heterogeneous, this study presents findings in by far the largest patient population evaluated prospectively. It is also unique in that it is based on observations from many different centers and countries, which in fact also may be considered of value. It should be noted, however, that almost two thirds of the pregnancies came from Italy, Scandinavia, and Australia, and 12 countries accounted for more than 90% of the cases (see table 1).

A limitation of EURAP is that seizure frequencies are only recorded by categories, and no information is collected on seizure control before pregnancy. Thus, we cannot assess fully the effect of pregnancy on seizure control, but rather describe seizure frequency categories during pregnancy and compare them between trimesters. This fact, of course, also hampers a comparison with previous reports. However, in studies providing a baseline assessment, this was usually obtained in retrospect with all inherent problems of recollection bias and lack of accuracy. The fact that almost 60% of our cases were seizure-free throughout pregnancy suggests that the EURAP cohort is less biased toward more severe epilepsy than are most previous studies of this kind. This high proportion of seizure-free patients is well in line with observations from some of the previous population-based studies.[7-9] The use of monotherapy in about 80% of the pregnancies points in the same direction.

We used seizure frequency in the first trimester as reference in the present study. It should be acknowledged that this period in fact to a variable extent is retrospective since cases could be enrolled as late as until week 16. Nevertheless, we found no difference between the second and the third trimesters with respect to risk of deterioration in seizure control from the first trimester. Previous studies have been conflicting on this issue. Some reported that the risk for deterioration is highest during the first trimester,[11,16,17] a possibility that could not be assessed in the present study. Others found the risk for increased seizures to be more pronounced during the last trimester.[7,9,18] In any case, our findings are in line with previous evidence suggesting that the majority of patients with epilepsy do not show a major change in seizure control during pregnancy, and that the proportions of those showing improvement or deterioration in seizure frequency during second or third trimester are evenly distributed.[6] Whether changes in seizure control observed in a minority of cases simply reflect random variation, or are a consequence of specific pathophysiologic changes associated with these pregnancies, remains a matter of speculation.

While there are conflicting data on changes in seizure frequency across each trimester, most studies are in agreement that labor and delivery carry a particularly high risk of seizure recurrence. Although there is a variation between studies, on average 5% of women with epilepsy have been reported to have seizures during labor, delivery, or the first 24 hours thereafter.[6,7,9,12,14,19-21] The incidence of seizures during this period has been estimated to be ninefold greater than during pregnancy in general.[7] In the present cohort, 3.5% experienced seizures during delivery, which is in agreement with previous publications. As expected, those seizure-free until delivery had the lowest risk of recurrence during delivery.

Status epilepticus occurred in almost 2% of the pregnancies, being convulsive in one third of the cases. In a review of studies up to 1980[6] it was concluded that fewer than 1% of women with epilepsy experience status epilepticus during pregnancy. This proportion was similar in publications between 1982 and 1994.[20] A 1% incidence is comparable to the inci-

dence of convulsive status in our cohort, an observation that suggests that nonconvulsive forms of status epilepticus, being less apparent, may have escaped diagnosis in earlier studies.

We were unable to identify any particular risk factor for the development of status epilepticus. The episodes were evenly distributed over the trimesters, and 53% of the women had had no seizures in their pregnancy when the status occurred. A more striking finding is that only one of the 36 cases of status ended in an overt adverse fetal outcome (stillbirth), and none was associated with maternal mortality. This finding is in contrast with previous results and with the prevailing opinion that status epilepticus during pregnancy is associated with a high fetal and maternal mortality. This opinion, in fact, is largely based on a review of 29 cases from the literature.[22] Among these 29 cases, there were 9 maternal deaths and 14 of the fetuses died in utero or shortly after birth. It is likely that this old case series assembled from small case reports suffers from publication bias favoring the reporting of adverse outcomes. The discrepancy between these reports and our results highlights the importance of conducting large prospective studies. It may also possibly reflect an improvement in the management of epilepsy in pregnancy during more recent years.

While this study included more than 700 patients with seizures during pregnancy, there was only one case where seizures seemed to be associated with a miscarriage (a case of status epilepticus) and none where a single discrete seizure was directly linked to miscarriage or stillbirth. Although it is difficult to exclude the possibility of delayed adverse fetal effects of seizures, it is noteworthy that seizure control in general did not seem to be worse in pregnancies ending in stillbirth or miscarriage than in other pregnancies. These observations should be comforting for women with epilepsy who consider pregnancy, although we did not assess in the present analysis the possible impact of maternal seizures on intrauterine fetal growth or on the risk of birth defects. However reassuring with respect to fetal risks associated with seizures, our results should not be interpreted as an argument against the use AEDs for the treatment of active epilepsy during pregnancy.

Our study also provides interesting information on therapeutic strategies and potential relationships among seizure control, AEDs used, and treatment changes during pregnancy. These data need to be interpreted with caution because EURAP is an observational study and treatments were not assigned by randomization. Drug choice is likely to be determined by the characteristics of the patient, including type of epilepsy, and we lack information on whether seizure control before pregnancy differed between treatment groups. Hence, our observation of complete control of convulsive seizures being less likely among those treated with oxcarbazepine should not be taken as evidence for an inferior efficacy of this drug during pregnancy. In particular, the small number of patients on oxcarbazepine, and the associated wider CI for this drug, call for additional interpretative caution. It is, however, intriguing that not only was complete seizure control less common with oxcarbazepine, but seizure deterioration after the first trimester and increases in AED number or dosage during pregnancy also occurred more frequently with oxcarbazepine. Increases in AED number or dosage were also significantly more common in women treated with lamotrigine. Despite the methodologic limitations, it is tempting to speculate that there could be specific mechanisms affecting the utilization of these drugs during pregnancy. In the case of lamotrigine, several independent studies have demonstrated a marked decrease in plasma drug levels during pregnancy.[23-27] Such a decrease appears to be more pronounced than that observed with other AEDs, and may result in seizure recurrence[27] and the need for more frequent dose adjustments. Although there are no sizable data on potential changes in oxcarbazepine pharmacokinetics during pregnancy, it is noteworthy that the active monohydroxy derivative of oxcarbazepine, which is mainly responsible for the drug's pharmacologic effect, shares with lamotrigine a primary route of elimination via glucuronidation.[28] It is therefore possible that pregnancy affects the metabolism of both drugs in a similar way, a hypothesis that needs to be tested in future studies. In general, our observations warrant further investigations, including separate comparisons for specific epilepsy syndromes taking into account the altered pharmacokinetics of AEDs in pregnancy.

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