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ORIGINAL COMMUNICATION

No increase in adverse pregnancy outcomes for women receiving antiepileptic drugs

Hsiu-Li Lin · Yi-Hua Chen · Hsiu-Chen Lin · Herng-Ching Lin

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Abstract The objectives of this study were (1) to investigate the incidence of adverse pregnancy outcomes among the epileptic and general populations, including small for gestational age (SGA), low birth weight (LBW) and preterm delivery, using two large-scale nationwide population-based databases, and (2) to compare the risk of these adverse pregnancy outcomes between epileptic women who did and who did not receive antiepileptic drug (AED) treatment during pregnancy. This study used two national datasets: the National Health Insurance Research Dataset and birth certificate registry. We identified a total of 1,182 women who gave birth from 2001 to 2003 in Taiwan who had been diagnosed with epilepsy within the 2 years preceding the index delivery, together with 5,910 matched women as a comparison cohort. Multivariate logistic regression analyses were performed for estimation of risk. We found that approximately 14% of women with epilepsy received AED treatment during gestation. The adjusted odds of LBW, preterm births and SGA for epileptic women not receiving AED treatment during pregnancy were 1.31 (95% CI, 1.02–1.68), 1.35 (95% CI, 1.07–1.71) and 1.23 (95% CI, 1.03–1.46) times that of women without epilepsy, respectively. In contrast, no significant difference in the risk of LBW infants, preterm births and SGA babies was observed between epileptic mothers receiving AED treatment during pregnancy and women without epilepsy. Our study documents an increased risk of adverse pregnancy outcomes for epileptic women who do not receive AED treatment during pregnancy, but none for epileptic women who do receive treatment.

Keywords Epilepsy · Pregnancy outcome · Preterm birth

H.-L. Lin
Department of Neurology, General Cathay Hospital, Sijhih Branch, Taipei, Taiwan

H.-L. Lin
Graduate School of Medical Informatics, Taipei Medical University, Taipei, Taiwan

Y.-H. Chen
Department of Public Health, Taipei Medical University, Taipei, Taiwan

Hsiu-Chen Lin
College of Medicine, Taipei Medical University, Taipei, Taiwan

Herng-Ching Lin (✉)
School of Health Care Administration, Taipei Medical University, 250 Wu-Hsing St, Taipei 110, Taiwan
e-mail: henry11111@tmu.edu.tw

Introduction

From the start of antiepileptic drug (AED) therapy in 1850, the goal of AED treatment has been freedom from seizures without significant adverse effects. However, women with epilepsy face the dilemma of continuing or discontinuing AED once they become aware of a pregnancy. Controlling maternal epilepsy and the development of the fetus have to be considered together in the decision to maintain AED treatment or not. In two recent studies, 49.7 to 53% of women with epilepsy had at least one seizure during pregnancy [1, 2]. Three earlier studies concluded that the condition of between 15 and 32% of women with epilepsy deteriorates during pregnancy [3–5]. Therefore, women with epilepsy should continue AED treatment to prevent seizures, though it is recommended they minimize dosages [6].

At the same time, potential adverse effects of AED therapy on the fetus should be considered. The fetal complications of maternal epilepsy range from malformation to milder ones, but increase childhood mortality and morbidity, including low birth weight (LBW), being small for gestational age (SGA) and preterm delivery [7, 8]. Major malformation was documented as being linked to AED exposure (especially polypharmacy and valproate) and may be dose related [4, 9–11]. However, the rate of LBW, SGA and preterm delivery among epileptic women is debated. Previous studies have produced contrary conclusions including increased risk, no difference and even decreased risk of these fetal complications among women with epilepsy [2, 4, 12, 13]. Studies based on voluntary registration have an inherent self-selection bias of design and tend to miss patients with low motivation to receive AED treatment and physician counseling, hence limiting our ability to draw conclusions from them [1, 2, 14].

The objectives of the present study were (1) to investigate the incidence of SGA, LBW and preterm delivery in the epileptic and general population, and (2) to compare the risk of adverse pregnancy outcomes among epileptic women who did and did not receive AED treatment during pregnancy, using two large-scale nationwide population-based datasets. Comparing pregnancy outcomes among women with epilepsy who do and do not receive AED treatment should provide insight into the roles of epilepsy and AED in inducing complications during pregnancy.

Methods

Databases

This study used two large-scale national datasets. First, we used data from the 1996–2003 National Health Insurance Research Dataset (NHIRD), published by the National Health Research Institute in Taiwan. The NHIRD consists of registries of contracted medical facilities, board-certified physicians and catastrophic illness patients, as well as a monthly summary of inpatient and ambulatory care claims for over 22 million enrollees, representing over 98% of the island's population. Although there are no documented sensitivity and specificity studies of coding accuracy, the data in the NHIRD are believed to be quite accurate because the government audits claims regularly. Fines for fraud are 100 times the amount of the false claim charged to the National Health Insurance Bureau. As a result, hospitals' interests are best served by accurate coding of diagnoses and care provided. Hundreds of researchers have used the NHIRD to perform studies and publish the findings.

The second database used in this study is the birth certificate registry published by Taiwan's Ministry of the Interior. The data on birth certificates include birth dates of both infants and parents, gestational week at birth, birth weight, gender, parity, place of birth, parental educational level and maternal marital status. Since the registration of all births is mandatory in Taiwan, its birth certificate data are considered to be extremely accurate and comprehensive.

With assistance from the Bureau of the National Health Insurance (NHI) in Taiwan, the mother's and infant's unique personal identification numbers provided links between the NHIRD and birth certificate data. Confidentiality assurances were addressed by abiding with the data regulations of the Bureau of NHI. All personal identifiers were encrypted by the Bureau of NHI before release to the researchers. Since the NHIRD consists of de-identified secondary data released to the public for research purposes, this study was exempt from full review by the Internal Review Board.

Study sample

There were 477,006 mothers with 588,499 singleton births in Taiwan between 1 January 2001 and 31 December 2003. If a mother had more than one singleton birth during the study period, we only selected the first for the study sample, because the inclusion of more than one pregnancy per woman in the analyses could influence the risk estimates. Ultimately, 473,529 women having 473,529 singleton live births fulfilled our criteria.

Our study includes a study cohort and a comparison cohort. The study cohort consists of all mothers who were diagnosed with a principal diagnosis of epilepsy. Of these 473,529 mothers, 2,504 were identified from inpatient or ambulatory care claims by a diagnosis of epilepsy (ICD-9 code 345) between 1998 and 2003. Since administrative databases are notorious for problems of coding validity, we ensured that all of the study cohort patients had at least three consensus diagnoses of epilepsy within 2 years prior to index delivery in order to ensure the validity of the diagnoses in this study. In addition, we excluded women diagnosed with other chronic diseases such as hypertension and diabetes that might affect pregnancy outcomes ($n = 10$), leaving a total of 1,182 women with epilepsy for analysis.

Our comparison cohort was extracted from the remaining 471,025 mothers. We excluded those mothers who had been diagnosed previously with any type of chronic disease other than epilepsy (such as hypertension, diabetes, systemic lupus erythematosus, rheumatoid arthritis, gout, sarcoidosis, or ankylosing spondylitis) between 1996 and 2003. We randomly selected 5,910 women (5 for every mother with epilepsy) matched with the study group in terms of age (<20, 20–24, 25–29, 30–34 and ≥35 years) and year of delivery.

Variables of interest

In this study, in addition to comparing pregnancy outcomes between women with epilepsy and women without epilepsy, we divided women with epilepsy into two categories: those receiving AED treatment during pregnancy and those not receiving AED treatment during pregnancy. At present, there is no definition of dosage that would define who is "on" or "off" medication for that time period. We defined those receiving AED treatment during pregnancy as women prescribed AED for more than 30 days.

The key dependent variables were whether an infant had LBW, preterm gestation, or was SGA. According the World Health Organization, the standard cutoff point for LBW is 2,500 g (<2,500 g, ≥2,500 g). Preterm birth was defined as birth occurring at a gestational age <37 weeks, and SGA was defined as birth weight below the tenth percentile for gestational age.

Other possible factors contributing to pregnancy outcome for infants were adjusted for in this study. These factors included characteristics of the infant (gender and parity), mother (age, the highest educational level and marital status), father (age and the highest educational level) and family monthly income (including mothers' and fathers' monthly incomes). Parental age was defined as each parent's age, in years, at the time of the infant's birth. Parity was grouped into the following categories: 1, 2, and ≥3. There were four maternal and paternal education levels: elementary school or lower, junior high school, senior high school, and college or above. The family monthly income variable was categorized into four groups: <NT$ 15,000, NT 15,000–30,000, NT 30,001–50,000 and ≥NT 50,001.

Statistical analysis

The SAS statistical package (SAS System for Windows, version 8.2) was used to perform the analyses in this study. Pearson χ^2 tests were used to examine the differences among epileptic mothers receiving AED treatment during pregnancy, epileptic mothers receiving no AED treatment during pregnancy and unaffected mothers in relation to infant characteristics, mother and father. Separate multivariate logistic regression analyses were also performed to explore the risk of LBW, preterm gestation and SGA for epileptic mothers receiving AED treatment during pregnancy, epileptic mothers receiving no AED treatment and unaffected mothers, after adjusting for the potential confounders. We found that there is a strong collinearity between maternal and paternal age, so we kept only maternal age in the regression model. In addition, we adjusted for age differences between parents. A two-sided p-value of <0.05 was considered statistically significant for this study.

Results

Of the total 1,182 epileptic women, 166 (14.0%) received AED treatment during pregnancy. The mean number of prescription days was 187 (standard deviation = 115 days), with 93 of the women who received AED during pregnancy (56.0%) starting during their first trimester. The gestational ages for all sampled women were older than 24 weeks. Table 1 describes epilepsy diagnoses and the type of anti-epileptic drug used for epileptic women. Among 1,182 epileptic women, more than half (63.5%) were diagnosed with generalized seizures. Table 2 presents the details of the distribution of characteristics of infants, mothers and fathers, comparing epileptic women receiving AED treatment during pregnancy, epileptic women not receiving AED treatment during pregnancy and unaffected women. Pearson χ^2 tests show that there were significant sociodemographic differences among these three groups of women in terms of highest maternal educational level ($p < 0.001$), family monthly income ($p < 0.001$), paternal age ($p = 0.039$) and highest paternal educational level ($p < 0.012$).

Table 3 describes the distribution and crude odds ratios of LBW, preterm birth and SGA for the three groups of women. Pearson χ^2 tests show that there were significant differences in LBW ($p = 0.048$), preterm birth ($p = 0.019$) and SGA ($p = 0.005$) among these women. The regression analyses show that epileptic women receiving no AED treatment during pregnancy were more likely to have LBW infants (OR = 1.36, 95% CI = 1.06–1.74), preterm births (OR = 1.38, 95% CI = 1.10–1.74) and SGA babies (OR = 1.27, 95% CI = 1.07–1.51) than unaffected mothers. In contrast, there was no significant difference in the risk of LBW infants, preterm births and SGA babies between epileptic women who received AED treatment during pregnancy and women without epilepsy.

Table 1 Epilepsy diagnoses and the type of anti-epileptic drug used for pregnant women with epilepsy in Taiwan, 2001–2003

Variable	*n* (%)
Diagnosis	
Partial seizures (ICD-9-CM codes 345.4–345.5, 345.7)	82 (6.9)
Generalized seizures (ICD-9-CM codes 345.0–345.3)	750 (63.5)
Unclassified epileptic seizures (ICD-9-CO codes 345.8–345.9)	350 (29.6)
Total	1,182
Drug type	
Phenytoin	77 (46.5)
Phenobarbital	8 (4.8)
Carbamazepine	9 (5.4)
Valproate	72 (43.3)
Total	166

Table 2 Comparison of maternal, paternal and infant characteristics among pregnant women with no chronic disease, pregnant women with epilepsy receiving anti-epileptic drug therapy and those not receiving drug therapy in Taiwan, 2001–2003 (n = 7,092)

Variable	Pregnant women with no history of chronic disease n = 5,910		Pregnant women with epilepsy not receiving treatment during pregnancy n = 1,016		Pregnant women with epilepsy receiving treatment during pregnancy n = 166	
	Total no.	%	Total no.	%	Total no.	%
Infant characteristics						
Gender						
Male	3,066	51.9	526	51.8	78	47.0
Female	2,844	48.1	490	48.2	88	53.0
Parity						
1	2,935	49.7	551	54.2	81	48.8
2	2,164	36.6	338	33.3	56	33.7
3 or more	811	13.7	127	12.5	29	17.5
Maternal characteristics						
Age						
<20	280	4.7	52	5.1	4	2.4
20–24	1,500	25.4	257	25.3	43	25.9
25–29	2,255	38.2	384	37.8	67	40.4
30–34	1,435	24.3	248	24.4	39	23.5
>34	440	7.4	75	7.4	13	7.8
Education level						
Elementary school or lower	114	1.9	26	2.6	5	3.0
Junior high school	934	15.8	199	19.6	41	24.7
Senior high school	4,112	69.6	685	67.4	106	63.9
College or above	750	12.7	106	10.4	14	8.4
Marital status						
Married	5,731	96.7	974	95.9	162	97.6
Others	179	3.3	42	4.1	4	2.4
Family monthly income						
<NT$15,000	2,372	40.1	409	40.3	58	34.9
NT$15,000–30,000	1,478	25.0	280	27.6	28	16.9
NT$30,001– 50,000	1,363	23.1	250	24.6	66	39.8
>NT$50,000	697	11.8	77	7.6	14	8.4
Paternal characteristics						
Age						
<30	54	0.9	6	0.6	1	0.6
20–34	4,676	79.1	790	77.8	117	70.5
>34	1,180	19.9	220	21.7	48	28.9
Education level						
Elementary school or lower	97	1.6	23	2.3	5	3.0
Junior high school	1,102	18.7	230	22.6	38	22.9
Senior high school	3,787	64.1	629	61.9	101	60.8
College or above	924	15.6	134	13.2	22	13.3

Details of the adjusted OR for LBW, preterm birth and SGA for each group of women are provided in Table 4. As the table shows, after adjusting for the infant's gender, parity, maternal age, highest maternal and paternal educational level (separately), parental age difference, mothers' marital status and family monthly income, the odds of LBW for epileptic mothers receiving no AED treatment during pregnancy were 1.31 times (95% CI = 1.02–1.68) that of women without epilepsy. In terms of preterm births and SGA, the adjusted odds ratios were

Table 3 Crude odds ratios for LBW, preterm birth and SGA infants among women with epilepsy and with no history of chronic disease, 2001–2003

Variable	No history of chronic disease $n = 5{,}910$		Epilepsy not treated during pregnancy $n = 1{,}016$		Epilepsy treated during pregnancy $n = 166$	
	No.	%	No.	%	No.	%
Low birth weight						
Yes	368	6.2	84	8.3	12	7.2
No	5,542	93.8	932	91.7	154	92.8
Crude HR (95% CI)	1.00		1.36* (1.06–1.74)		1.17 (0.65–2.13)	
Preterm birth						
Yes	433	7.3	100	9.8	14	8.4
No	5,477	92.7	916	90.2	152	91.6
Crude HR (95% CI)	1.00		1.38** (1.10–1.74)		1.17 (0.62–2.03)	
Small for gestational age						
Yes	951	16.1	199	19.6	36	21.7
No	4,959	83.9	817	80.4	130	78.3
Crude HR (95% CI)	1.00		1.27** (1.07–1.51)		1.45 (0.98–2.10)	

*$p < 0.05$; **$p < 0.01$; odds ratios (OR) are unadjusted

1.35 (95% CI, 1.07–1.71) and 1.23 (95% CI, 1.03–1.46), respectively, for epileptic mothers receiving no AED treatment during pregnancy compared to mothers in the comparison cohort.

Discussion

Our nationwide population-based study compared three neonatal outcomes: low birth weight (LBW), preterm delivery and small for gestation age (SGA) among epileptic women and women in the general population in Taiwan in 2001–2003. The cohort of women with epilepsy was further divided into two subgroups: those receiving AED treatment (14%) and those who did not (86%). Of the total 473,529 women, 2,504 (0.53%) were identified as having epilepsy, consistent with epidemiological findings of 0.3–0.5% in the US, 0.7% in a Finnish community-based study by Viinikainen and 0.5% in Richmond's hospital-based study in Canada, but lower than the 3.3% found by Olafsson's nationwide study of the Icelandic population [4, 13, 15, 16].

We found the risks of having LBW infants, preterm delivery and infants with SGA among epileptic mothers receiving no AED treatment were higher than among women without epilepsy: the adjusted odds ratios were 1.31, 1.35 and 1.23 for LBW, preterm babies and SGA, respectively. However, there was no difference in fetal complications when comparing epileptic mothers receiving AED treatment and women without epilepsy. This suggests that women with epilepsy have a greater tendency to have LBW, preterm and SGA babies, but this adverse effect can be counteracted by AED therapy.

It has been widely believed that there tends to be more unfavorable outcomes among babies of epileptic mothers, which could result from genetics, seizures during pregnancy or AED exposure. To assess whether this is so, environmental factors including mothers' nutrition, smoking habits, knowledge of self-care and socioeconomic support should be considered.

Since the 1980s, several studies have been performed to investigate the relationship between epilepsy and fetal complications; however, conflicting conclusions were obtained, apart from major congenital complications. Hiilesmaa et al. [12] observed a higher rate of SGA and preterm births among women with epilepsy. Hvas et al. [11] reported an increased risk of LBW and infants SGA among women with epilepsy. Viinikainen et al. [15] concluded there was no difference in preterm and LBW infants between women with epilepsy and the normal population, but there was a higher rate of infant SGA among the women with epilepsy. On the other hand, Richmond et al. and Saleh et al. [4, 17] reported no differences in the rate of preterm deliveries and birth weight. Olafsson [13] also reported no difference in birth weight and gestation age. In a hospital case series, Katz et al. [7] reported similar mean birth weights and gestational ages, regardless of AED usage. Thomas et al. [2] indicated that, contrary to general belief, there were fewer LBW deliveries among women with epilepsy. These inconsistent conclusions may be explained by patient selection, the percentage receiving AED treatment and failure to adjust for potential confounders.

In this study based on a nationwide population, only 166 (14%) women received AED treatment for over 30 days during pregnancy. This percentage is obviously lower than

Table 4 Adjusted odds ratios of LBW, preterm birth and SGA infants for women with epilepsy and women with no history of chronic disease in Taiwan ($n = 7{,}092$)

Variable	Low birth weight Adjusted OR, 95% CI	Preterm birth Adjusted OR, 95% CI	Small for gestational age Adjusted OR, 95% CI
Women with			
Epilepsy not treated during pregnancy	1.31* (1.02–1.68)	1.35* (1.07–1.71)	1.23* (1.03–1.46)
Epilepsy treated during pregnancy	1.13 (0.62–2.06)	1.14 (0.65–2.00)	1.38 (0.94–2.02)
No history of chronic disease	1.00	1.00	1.00
Maternal characteristics			
Age (years)			
<20	1.00	1.00	1.00
20–24	0.67* (0.45–0.99	0.93 (0.62–1.41)	0.70* (0.53–0.93)
25–29	0.56** (0.37–0.87)	0.73 (0.47–1.13)	0.59*** (0.44–0.79)
30–34	0.63 (0.39–1.02)	1.04 (0.65–1.67)	0.65* (0.47–0.91)
>34	0.87 (0.50–1.51)	1.09 (0.63–1.88)	0.72 (0.48–1.06)
Education level			
Elementary school or lower	1.12 (0.62–2.00)	0.75 (0.40–1.41)	0.87 (0.56–1.36)
Junior high school	0.90 (0.69–1.17)	1.10 (0.87–1.40)	0.96 (0.80–1.14)
Senior high school	1.00	1.00	1.00
College or above	0.70 (0.47–1.04)	0.92 (0.65–1.29)	0.68** (0.53–0.87)
Marital status			
Married	1.00	1.00	1.00
Others	1.47 (0.94–2.28)	1.44 (0.94–2.21)	1.63** (1.19–2.22)
Infant characteristics			
Gender			
Male	0.86 (0.71–1.03)	1.56*** (1.30–1.86)	0.68*** (0.60–0.77)
Female	1.00	1.00	1.00
Parity			
1	1.00	1.00	1.00
2	0.88 (0.70–1.09)	1.05 (0.86–1.29)	0.88 (0.76–1.01)
3 or more	1.01 (0.74–1.31)	1.42* (1.08–1.86)	0.84 (0.68–1.04)
Family monthly income			
<NT$ 15,000	1.00	1.00	1.00
NT$ 15,000–30,000	0.96 (0.73–1.26)	0.78 (0.61–1.01)	0.93 (0.78–1.11)
NT$ 30,001–50,000	1.03 (0.78–1.38)	0.87 (0.66–1.13)	1.05 (0.87–1.27)
>NT$ 50,000	0.83 (0.55–1.24)	0.77 (0.54–1.10)	0.80 (0.61–1.04)
Parental age difference	1.02 (0.99–1.04)	0.99 (0.97–1.02)	1.01 (0.99–1.03)
Paternal characteristics			
Education level			
Elementary school or lower	2.12** (1.24–3.61)	1.98* (1.16–3.39)	1.79** (1.17–2.72)
Junior high school	1.02 (0.80–1.31)	1.23 (0.99–1.54)	1.10 (0.93–1.29)
Senior high school	1.00	1.00	1.00
College or above	0.91 (0.65–1.28)	0.93 (0.68–1.27)	1.01 (0.81–1.26)

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

that in previous registry-based or hospital-based studies, ranging from the 45% reported by Hvas et al. in Denmark, 90% reported by Chang et al. in Taiwan, to 100% reported by Saleh in Saudi Arabia [12, 14, 17]. This illustrates the self-selection bias disadvantage of registry systems, which may miss a large number of epileptic women with low motivation to receive counseling and to control their epilepsy. Furthermore, the mean AED prescription duration for these 166 epileptic mothers was 187 ± 115 days, with 93 of them (56%) taking AED in the first trimester.

It appeared that those who took AED in the early months of pregnancy tended to adhere to the medication up to delivery. Those who did not take AED initially, conversely, would not receive AED during the whole period of pregnancy. Accordingly, the conclusions coming from registry- and hospital-based studies have to be adopted cautiously when considering an epileptic population with poor to moderate compliance with AED therapy.

The low percentage of women with epilepsy who received AED treatments during pregnancy in our study deserves more attention. In Taiwan, physicians prescribe appropriate medication by considering patient needs given their diseases and the FDA's Pregnancy Drug Categories (proposed by the Food and Drug Administration in the USA). As all commonly used AEDs are teratogenic to some degree, most women in Taiwan are more conservative and thus reluctant to take medicine during pregnancy out of concern for adverse fetal development [18, 19]. Both physicians and patients should consider balancing the fetal risk from uncontrolled epilepsy against the potential adverse effects of AED.

In two prior studies, epileptic mothers were evaluated as a whole group, no matter whether they were taking AED treatment or not [4, 13]. The difference in the fatal complication rate may be offset by the different percentage receiving AED comparing the groups. However, there are three studies comparing the difference between pregnant women receiving and not receiving AED treatment [7, 12, 15]. Katz et al. found no difference in birth weight and SGA infants between those on or not on AED therapy, and between pregnancies with seizures occurring or seizure-free pregnancies. But they had a small sample size of 100 cases observed and only 10 women with epilepsy in the group not receiving AED. One study by Hvas was based on data collected from questionnaire survey. However, if seizure frequency and fetal birth weight depend on mothers' recall, precision may be questioned. In addition, another study by Viinikainen failed to adjust for patients' socioeconomic status.

Using a nationwide database, our study has the advantages of a large sample size and representing the actual distribution of women with epilepsy and AED compliance. This avoids problems of selection bias inherent to voluntary registries or hospital-referred study patients. Additionally, we included and adjusted for the socioeconomic and other potentially confounding variables to avoid misleading results.

Nevertheless, since the dataset for this study is based on claims data of the Bureau of National Health Insurance, it necessarily lacks clinical records of seizure events and the reason for switching to or from AED therapy. To clearly assess the association between AED treatments and pregnancy outcomes, women with epilepsy who were diagnosed with other chronic diseases such as hypertension and diabetes were excluded. While similar exclusion criteria applied in selecting the comparison cohort for comparability, we might thus examine a healthier population. In addition, information on smoking, alcohol consumption, substance abuse and the nutritional state of mothers are not available. These factors affect the risk of adverse pregnancy outcomes. Further investigation that takes into account seizure frequency during pregnancy and adjusted fetal outcomes is required to validate our findings and advance our knowledge of how to care for pregnant women with epilepsy.

In conclusion, we found that epileptic women not receiving AED treatment during pregnancy tended to have more adverse pregnancy outcomes than women without epilepsy. However, there was no significant difference in the risk of adverse pregnancy outcomes between epileptic women receiving AED treatment during pregnancy and women without epilepsy. This suggests that women with epilepsy will deliver more babies with fetal complications if they do not receive AED treatment. Therefore, the risk of malformation and seizure prevention benefit of AED have to be reconsidered. Since only 14% of pregnant women with epilepsy receive AED treatment in Taiwan, action should be taken to provide better pregnancy counseling and further evaluate the effects of AED treatment.

Conflict of interest statement None.

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