Clinical Characteristics of Pregnant Women With Epilepsy-A Retrospective Multi Center Study

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Abstract

**Background:** Many women with epilepsy (WWE) become pregnant, so the control of seizures during pregnancy and the use of anti-epileptic drugs (AEDs) may directly affect the outcome of pregnancy. This study retrospectively analyzed seizures, medications, and pregnancy outcomes of WWE, in order to provide clinical basis for reasonable management of pregnancy in these women.

**Methods:** Information, including seizures, medications during pregnancy and pregnancy outcomes of WWE, was collected through telephonic follow-up and retrospectively analyzed.

**Results:** Among the 61 WWE, 26 cases had seizures during pregnancy. Among the WWE treated with monotherapy, the most commonly used AEDs were carbamazepine (29.27%), levetiracetam (31.71%) and lamotrigine (14.63%). Nine WWE had adverse pregnancy outcomes. The incidence of adverse pregnancy outcomes in WWE who had seizures within one year before pregnancy was significantly higher than WWE who were seizure-free within one year before pregnancy ($c^2=5.355$, $p=0.021$). The incidence of adverse pregnancy outcomes in WWE who had seizures during pregnancy was also significantly higher than WWE without seizures during pregnancy ($c^2=7.155$, $p=0.007$).

**Conclusions:** A small number of WWE had adverse pregnancy outcomes, while the majority of them had relatively stable epilepsy control during pregnancy and gave birth to a healthy offspring. The main therapeutic drugs for WWE are new AEDs, represented by levetiracetam and lamotrigine, and the use of valproate sodium has been significantly reduced. Seizures within one year before pregnancy may be able to predict seizures during pregnancy.

**Background**

Due to changes in hormone levels, pharmacokinetics of anti-epileptic drugs (AEDs), and blood concentration of AEDs during pregnancy\[1, 2\], the control of seizures during pregnancy in women with epilepsy (WWE) may be affected, which further affects their pregnancy outcomes. Numerous studies are focusing on the physiological period of epilepsy combined with pregnancy, hoping to provide strategies for the management of WWE during pregnancy, in order to protect the health of pregnant women and their fetuses.

**Methods**

WWE who had given birth between 2013 and 2018 at the Epilepsy Center and Department of Obstetrics, Xinhua Hospital, Shanghai Jiaotong University School of Medicine and Epilepsy Center of Huashan Hospital, Fudan University were retrospectively enrolled in this study, and their data was collected through the electronic medical record system, telephonic follow-up, and the general condition survey form. The age range of the participants was 18–49 years when they were pregnant. These patients were diagnosed with epilepsy by neurologists, and the diagnosis was based on clinical seizures and/or various epileptiform discharges found on electroencephalogram. All participants volunteered to participate in this
survey. WWE with a history of intellectual disability or mental disorders, and the inability to communicate normally with the investigator were excluded. SPSS 19.0 statistical software was used for statistical analysis. Normally distributed measurement data was expressed as counting data by rate or composition ratio. Comparison of enumeration data between different groups was performed by chi-square test or Fisher's exact probability method. A p < 0.05 indicated that the difference was statistically significant.

Results

Data of 61 WWE were collected. Among all, 49 WWE came from Epilepsy Center of Xinhua Hospital, Shanghai Jiaotong University School of Medicine, 12 came from Epilepsy Center of Huashan Hospital, Fudan University. Their age at pregnancy ranged from 19 to 42 years. Tables 1 and 2 summarize the demographic characteristics, seizure type, status epilepticus, medication and epileptic frequency of the participants.
| Items                      | Number | Portion(%) | Mean  | SD  | Range |
|----------------------------|--------|------------|-------|-----|-------|
| Age of onset               | -      | -          | 15.61 | 6.4 | 5–28  |
| Gestational age            | -      | -          | 35.57 | 2.62| -     |
| Age of pregnancy (years)   | -      | -          | 28.69 | 3.72| 19–42 |
| 18–27                      | 19     | 31.1       | -     | -   | -     |
| 28–37                      | 41     | 67.2       | -     | -   | -     |
| 38–47                      | 1      | 1.6        | -     | -   | -     |
| Hometown                   | -      | -          | -     | -   | -     |
| Shanghai                   | 52     | 85.2       | -     | -   | -     |
| Zhejiang and Jiangsu       | 9      | 14.8       | -     | -   | -     |
| Pregnancy times            | -      | -          | -     | -   | -     |
| 1                          | 45     | 72.5       | -     | -   | -     |
| 2                          | 11     | 27.5       | -     | -   | -     |
| Education                  | -      | -          | -     | -   | -     |
| Primary school             | 2      | 3.3        | -     | -   | -     |
| Junior middle school       | 3      | 4.9        | -     | -   | -     |
| Senior middle school       | 14     | 23         | -     | -   | -     |
| College or above           | 42     | 68.9       | -     | -   | -     |
| Employment                 | -      | -          | -     | -   | -     |
| Unemployed                 | 6      | 9.8        | -     | -   | -     |
| Employed                   | 55     | 90.2       | -     | -   | -     |
| Seizure type               | -      | -          | -     | -   | -     |
| Generalized seizure        | 45     | 73.8       | -     | -   | -     |
| Partial seizure            | 9      | 14.8       | -     | -   | -     |
| Unclassified seizure       | 7      | 11.5       | -     | -   | -     |
| Status epilepticus         | 59     | 96.7       | -     | -   | -     |
|                            | 2      | 3.3        | -     | -   | -     |

SD = standard deviation.
Comparison of the epileptic seizures of WWE within one year before pregnancy, during pregnancy, and within one year after delivery showed that most WWE had seizures during pregnancy, 23 WWE had seizures within one year before pregnancy, 17 patients had epileptic recurrence during pregnancy; 38
WWE were seizure-free within one year before pregnancy, nine patients had epileptic recurrence during pregnancy. Analysis (Table 3) showed that WWE who had seizures within one year before pregnancy were significantly more likely to have seizures during pregnancy ($c^2 = 14.781, p = 0.000$).

| Predictors of seizures during pregnancy | Seizures within one year pre-pregnancy | Taking AED | Polytherapy | Taking Traditional AED | Reducing medication by self |
|---------------------------------------|---------------------------------------|------------|------------|------------------------|---------------------------|
|                                         | Yes No                                | Yes No     | Yes No     | Yes No                 | Yes No                    |
| Yes                                    | 17 9                                  | 23 3       | 8 15       | 5 10                   | 5 21                      |
| No                                     | 6 29                                  | 29 6       | 3 26       | 9 17                   | 1 34                      |
| $c^2$                                  | 14.781                                | 0.060      | 3.244      | 0.007                  | 2.852                     |
| p-value                                | 0.000                                 | 0.806      | 0.072      | 0.934                  | 0.091                     |

In terms of AED therapy during pregnancy, 41 WWE received monotherapy and 11 WWE received polytherapy. Among the WWE treated with monotherapy, the most commonly used AED was carbamazepine, which did not change significantly before and after pregnancy; the second was levetiracetam, which was used more during pregnancy. Meanwhile, sodium valproate was used less during pregnancy (Fig. 1).

Among the 61 WWE, 59 cases successfully delivered, while two cases were induced. Among them, most patients achieved term pregnancy, only four cases gave birth prematurely. There were 56 cases with normal birth weight and three cases with low birth weight. Most newborns were born with an Apgar score $> 7$ points and only two newborns were born with an Apgar score $\leq 7$ points. We found that 45 cases chose cesarean section, while 14 cases gave birth naturally. Moreover, nine cases had adverse pregnancy outcomes, including premature births (6.6%), low birth weight (4.9%), newborns with Apgar score $< 7$ points (3.3%), induced labor (3.3%) and prenatal hemorrhage (1.64%). There was no obvious abnormality in the growth and development of newborns (Table 4).
WWE with seizures within one year before pregnancy had a significantly higher probability of adverse pregnancy outcomes than those without seizures within one year before pregnancy ($c^2 = 5.355, p = 0.021$). The probability of adverse pregnancy outcomes in WWE with seizures during pregnancy was also significantly higher than those without seizures during pregnancy ($c^2 = 7.155, p = 0.007$). These results indicated that control of seizures has an important impact on pregnancy outcomes of WWE. WWE taking AED were more likely to have adverse pregnancy outcomes, although the difference was not statistically significant. Moreover, WWE treated with polytherapy and traditional AED were more likely to have adverse

| Items                                | Number | Portion (%) |
|--------------------------------------|--------|-------------|
| Live fetus                           |        |             |
| Yes                                  | 59     | 96.72       |
| No                                   | 2      | 3.28        |
| Premature delivery                   |        |             |
| Yes                                  | 4      | 6.6         |
| No                                   | 55     | 90.2        |
| Low birth weight                     |        |             |
| Yes                                  | 3      | 4.90        |
| No                                   | 56     | 91.8        |
| Apgar score                          |        |             |
| > 7                                  | 57     | 93.4        |
| ≤ 7                                  | 2      | 3.3         |
| Delivery method                      |        |             |
| Natural childbirth                   | 14     | 23          |
| Cesarean section                     | 45     | 73.8        |
| Adverse pregnancy outcomes          |        |             |
| Yes                                  | 9      | 14.8        |
| No                                   | 52     | 85.2        |
| Neonatal development                 |        |             |
| Normal                               | 59     | 100%        |
| Abnormal                             | 0      | 0%          |
pregnancy outcomes than WWE treated with monotherapy and new AED, but the difference was not statistically significant (Table 5).

Table 5
Possible factors influencing adverse pregnancy outcomes

|                        | Seizures within one year pre-pregnancy | Seizures during pregnancy | Taking AEDs | Polytherapy | Taking traditional AEDs |
|------------------------|----------------------------------------|---------------------------|-------------|-------------|------------------------|
| Adverse pregnancy outcomes | Yes No                                 | Yes No                    | Yes No      | Yes No      | Yes No                 |
| Yes                    | 7 2                                    | 8 1                       | 8 1         | 3 5         | 2 3                    |
| No                     | 16 36                                  | 18 34                     | 44 8        | 8 36        | 12 24                  |
| c²                     | 5.355                                  | 7.155                     | 0.000       | 0.578       | 0.000                  |
| p-value                | 0.021                                  | 0.007                     | 1.000       | 0.447       | 1.000                  |

Discussion

Among the 61 WWE included in this study, 57.4% were seizure-free during pregnancy. Thomas SV [3] reported a proportion of 47.8%, while Battino D [4] and Galappatthy P [5] reported 66.6% and 64%, respectively, so our finding was within the above range, with no significant difference. In addition, 73.8% of WWE had no significant changes in epileptic frequency. Therefore, even if WWE have special physiological changes during pregnancy, epileptic frequency during pregnancy is not affected in most patients. Although 15 WWE had an increased frequency of seizures during pregnancy in this study, there is currently insufficient evidence that pregnancy can induce seizures or affect epileptic frequency [6].

Most WWE could take AED regularly during pregnancy. Only a small number of WWE adjusted AED dose or type when they were pregnant, and during follow-up, it was found that these WWE generally considered that AED may have side effects on the fetus. However, they ignored the greater risk that epileptic seizures may bring to the fetus. There is insufficient awareness of the risk of adverse pregnancy outcomes, and the initiative of treatment is not high. Therefore, clinicians need to educate the WWE to make them realize the importance of seizure control for themselves and their fetuses.

This study found that new AEDs such as levetiracetam and lamotrigine are increasingly used, while sodium valproate has gradually been reduced during pregnancy. As levetiracetam and lamotrigine are currently recognized to have the least impact on fetal teratogenicity [6], they have become the most commonly used AEDs for women of childbearing age. Sodium valproate has significant teratogenicity to the fetus, and an obvious impact on the cognitive function of newborns [7, 8]. Although sodium valproate is effective in treatment of epilepsy, clinicians do not consider it as the first choice in treatment of WWE of childbearing age. Especially for WWE during pregnancy, given the relatively high teratogenicity risk of
traditional AEDs to the fetus, the new AEDs have been used as the main drugs in WWE of childbearing age. As a traditional AED, carbamazepine has higher teratogenicity than new AEDs. However, in this study, carbamazepine was the most commonly used AED during pregnancy, and similar results were observed in previous studies\cite{6,9}, which may be due to different types of epileptic seizures, and the rate of use in this study was based on monotherapy. Patients who did not take AED or were treated with polytherapy were excluded, resulting in a smaller sample size and higher utilization of carbamazepine.

The cesarean section rate of WWE is higher than the general population\cite{10-12}. In 2014, China's Maternal and Child Health Annual Report mentioned that the cesarean section rate in China was 35%. In this study, the cesarean section rate of WWE was 73.8%, which was significantly higher. Such a high cesarean section rate may be related to the following factors: due to social trends, increasing number of pregnant women choose cesarean section to reduce the pain during childbirth, and this trend is particularly obvious among urban women. Patients in this study were all from developed coastal areas such as Shanghai, Jiangsu and Zhejiang provinces, so the difference may be even greater. Moreover, obstetricians may worry about sudden seizures during natural childbirth, leading to adverse pregnancy outcomes for the mother and baby, and therefore recommend patients to have a cesarean section, which may have led to an obvious difference in this study given the small sample size.

Although most WWE can give birth smoothly\cite{13} and most of their babies are healthy\cite{10}, the risk of adverse pregnancy outcomes in these patients is higher than the general population\cite{14,15}. The main adverse pregnancy outcomes include spontaneous abortion, infants below gestational age, premature infants, low birth weight infants, and pre-eclampsia. Other adverse pregnancy outcomes include induction of labor, prenatal hemorrhage, postpartum hemorrhage, low Apgar score (< 7 points) and fetal loss (fetal death after 20 weeks of pregnancy). In this study, the probability of adverse pregnancy outcomes was 14.8%, which was lower than previously reported\cite{15}. Seizures and medication may have caused this difference.

We compared seizures before pregnancy, seizures during pregnancy, as well as medications between WWE with adverse pregnancy outcomes and WWE with normal pregnancy outcomes. It was found that whether AED was taken during pregnancy had no effects on pregnancy outcomes of WWE, which is consistent with a previous study\cite{15}. It is currently believed that polytherapy and traditional AEDs are teratogenic to fetuses of WWE. The malformation of fetuses is closely related to adverse pregnancy outcomes. Therefore, polytherapy and traditional AEDs have an impact on adverse pregnancy outcomes. However, this study did not show similar findings, which may be because the majority of WWE took monotherapy and new AEDs. Monotherapy and new AEDs are widely used for WWE of childbearing age, and well recognized by clinicians.

However, this study also found that WWE have a significantly higher probability of adverse pregnancy outcomes. A previous study showed that epileptic seizures during pregnancy can lead to increased mortality in patients, and the risk of adverse pregnancy outcomes was also higher than the general
population\textsuperscript{[16]}. Therefore, the control of seizures during pregnancy is directly related to the health of mothers and babies.

In addition, this study found that epilepsy within one year before pregnancy had a statistically significant effect on pregnancy outcomes. This may be because seizures within one year before pregnancy can predict epileptic recurrence during pregnancy. Hence, we analyzed the factors that may predict seizures during pregnancy, and found that taking AEDs during pregnancy and the number of AEDs had no predictive effects on seizures during pregnancy. A previous study found that WWE who were not treated with AED during pregnancy and those who were treated with polytherapy were more likely to have seizures during pregnancy\textsuperscript{[17]}. There were fewer patients who did not receive AED and polytherapy in this study, which is inconsistent with the previous study result.

Meanwhile, changes in pharmacokinetics of AEDs during pregnancy may lead to lower drug concentrations in the blood, and increase the risk of seizures during pregnancy\textsuperscript{[2]}, especially for new AEDs such as lamotrigine and levetiracetam. Blood concentration of lamotrigine was found to be decreased most significantly during pregnancy, and WWE taking lamotrigine were more likely to have seizures during pregnancy\textsuperscript{[4]}. Therefore, we compared and analyzed WWE taking traditional AEDs and new AEDs, and found that although WWE taking new AEDs were more likely to have seizures during pregnancy than those taking traditional AEDs, there was no statistical significance. Therefore, AED type cannot be used as a predictor of seizures during pregnancy. Additionally, WWE who took new AEDs did not monitor blood drug concentration, so it was not considered that seizures of these patients during pregnancy were caused by decrease of AED concentration. Consequently, we recommend that WWE taking lamotrigine, levetiracetam and other new AEDs should undergo regular blood drug concentration monitoring if they have frequent seizures during pregnancy.

It was also found that WWE who reduced medication by themselves during pregnancy had a higher probability of seizures than those taking AED regularly, but it was not statistically significant after analysis, although patients’ compliance in this study did not predict seizures during pregnancy. We do not recommend that patients reduce AED dose or switch AED type after confirming their pregnancy. They should consult a clinician and obtain a reasonable treatment plan after comprehensive evaluation.

Seizures within one year before pregnancy is called active epilepsy, and seizure-free for more than one year is called inactive epilepsy, and active epilepsy is considered to be an important predictor of seizures during pregnancy\textsuperscript{[17]}, which is consistent with the result of our study. Therefore, if WWE plan to get pregnant, they must inform the clinician and adhere to outpatient follow-up, so as to develop a perfect treatment plan for epilepsy during pregnancy, and achieve safe and smooth delivery, ensuring the health of mothers and babies.

Even though fetuses exposed to AED have a higher rate of teratogenicity than normal fetuses, no fetal or neonatal abnormalities were found in this study. This could be due to the following reasons: the risk of teratogenicity in fetuses exposed to AED in utero is higher than normal fetuses, but the overall incidence
is small, and such statistics require multi-center and large samples. Studies have shown that WWE taking traditional AEDs during pregnancy, especially sodium valproate, may have cognitive impairment, developmental delay, and mental retardation in their offspring\cite{18,19}, so WWE chose to take lamotrigine, levetiracetam or other low-teratogenic new AEDs during pregnancy in this study, which further decreased the teratogenic rate of fetuses exposed to AEDs.

**Conclusions**

In summary, the majority of WWE showed no significant changes in epileptic frequency during pregnancy, and could take AED regularly, only few patients had poor compliance. Many pregnant WWE were treated with monotherapy, and they mainly took new AEDs. Traditional AED, especially sodium valproate was replaced by other AEDs in WWE of childbearing age. WWE could give birth smoothly to healthy babies. For WWE with poor pregnancy outcomes, seizures during pregnancy and seizures within one year before pregnancy were influencing factors, and seizures within one year before pregnancy was an important predictor of seizures during pregnancy. Therefore, pregnant WWE should adhere to AED therapy regularly. Controlling epileptic seizures can guarantee health of mothers and babies. However, due to the small sample size of this study, the results may not be representative. In the future, multi-center, large-sample clinical studies are needed to confirm these findings.

**Abbreviations**

AEDs, anti-epileptic drugs; WWE, women with epilepsy; VPA, valproate; CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; TPM, topiramate; PB, phenobarbitone; PHT, phenytoin sodium

**Declarations**

**Ethics approval and consent to participate**

This clinical study was a retrospective study. We only collected clinical data of the patients, did not do any treatment with the patients, and did not bring physiological risks to the patients. The researchers would do their best to protect the information provided by the patients from revealing personal privacy, and hereby apply for exemption of informed consent. The board of ethics committee “Xinhua Hospital Ethics Committee Affiliated to Shanghai Jiaotong University School of Medicine” agreed to the study work as planned.

**Consent to publish**

All authors provided written consent for publication.

**Availability of data and materials**
Characteristics of study population are included in the Tables and figure. Further data set could be obtained on request if required. Our data are deposited in our epilepsy center database. Further data used or analysed during the current study available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

**Clarification**

The survey hasn’t been published anywhere else.

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**Authors’ Contributions**

All authors did lots of efforts to this study. XHT and ZGL designed the original study. HC wrote the manuscript. DYW, LL, QYF, HC and XHT included the patients and analysed the data; XHT revised the manuscript and supervised the study. All authors gave their final approval to the study to be published and agree to be accountable for all aspects of the work.

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Figures
Figure 1
Comparison of monotherapy in WWE before and during pregnancy.

Figure 2
Comparison of traditional and new AEDs before and during pregnancy.