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Association of oxcarbazepine concentration with seizure frequency in pregnant women with epilepsy

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ABSTRACT

The management of epilepsy during pregnancy presents particular challenges for neurologists worldwide. Currently, there are no clear recommendations for oxcarbazepine (OXC) specific target concentration during pregnancy. We conducted this retrospective observational cohort study on pregnant women with epilepsy (WWE) who received OXC monotherapy or polytherapy, at the epilepsy outpatient clinic of a tertiary hospital in eastern China. Sixteen pregnancies of 16 WWE were split into the seizure-free group or the non-seizure-free group, according to whether they had been seizure free for more than one year prior to conception or not. There was a significantly decrease in OXC concentration throughout pregnancy, as indicated by the concentration/dose ratio and the ratio of target concentration (RTC). The second trimester of pregnancy was the period when seizure deterioration occurred the most, particularly in the non-seizure-free group. Lower RTC_OXC was identified to be a risk factor for increasing seizure frequency in both the total group and the non-seizure-free group in both univariate and multivariate analysis, with a threshold of 0.575 for differentiating patients at high-risk and low-risk for seizure deterioration. In conclusion, this study suggested an OXC concentration threshold of 0.575 during pregnancy for assisting neurologists in OXC drug monitoring and dose adaptation.

1. Introduction

Epilepsy is one of the most common chronic neurological disorders, among which 40 % women with epilepsy (WWE) are of reproductive age. The management of epilepsy during pregnancy and the perinatal period presents particular challenges for neurologists worldwide. The treatment must balance the potential teratogenicity, tolerability, adverse effects of anti-seizure medications (ASMs) with the risk of seizures [1]. The pronounced pharmacokinetic alterations of ASMs during pregnancy, including increased volume of distribution, elevated renal clearance, and induction of hepatic metabolism [2,3], further complicated management. The timing and range of ASMs dose adjustments can be guided by understanding the patterns of gestational age (GA)-dependent concentration variations. Therefore, therapeutic drug monitoring (TDM) during pregnancy is indicated to improve clinical outcomes [4,5].

The most widely used ASMs in Chinese patients were lamotrigine (LTG), levetiracetam (LEV), and oxcarbazepine (OXC), according to a recent study conducted in a tertiary hospital in China [6]. They were considered as ideal ASMs administered to pregnant WWE for higher effectiveness and safety [7,8]. The reduction in ASMs concentration is associated with an increase in seizure frequency during pregnancy, which has been clearly demonstrated in LTG, and similar relationships have been observed in LEV and OXC [9]. For LTG specifically, previous studies revealed that a concentration decline of more than 35 % is a significant predictor of increased seizure frequency [10,11]. Similarly, it was suggested that LEV concentrations in pregnancies that had a seizure within the preceding year maintain above 65 % of the preconception concentration. While for those who have been seizure-free for longer than 12 months, they recommended an LEV threshold of approximately 46 % [12].

OXC is among the first-line options for the initial treatment of focal-

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onset seizures in several countries, and many worldwide treatment guidelines list OXC as a second-line alternative for generalized onset tonic-clonic seizures (GTCS) [13]. It is rapidly absorbed and converted into 10,11-dihydro-10-hydroxycarbazepine (monohydroxy derivative, MHD), which is its main clinical active metabolite [14]. OXC is mainly excreted by the kidneys in the form of metabolites [15]. At present, the dosage adjustment of OXC in clinical practice is mainly based on its serum concentration and clinical manifestations. Many investigations have demonstrated that the concentration of OXC decreases by an average of 30 % −40 % during pregnancy [14]. However, the existing ASMs concentration thresholds at which patients are considered to be at risk for worsening seizures are based only on studies of patients using LTG or LEV. There are no clear recommendations for OXC-specific concentration threshold on seizure deterioration during pregnancy.

In this study, we aim to clarify the changes in OXC concentration in pregnant WWE in eastern China; to verify the association between decreased OXC concentration and increased seizure frequency during pregnancy; and to suggest a threshold value of OXC concentration for assisting neurologists in OXC drug monitoring and dose adaptation.

2. Materials and methods

2.1. Study design

We conducted a retrospective observational cohort study on pregnant WWE who were routinely monitored at the epilepsy outpatient clinic of the Second Affiliated Hospital of Zhejiang University School of Medicine. This study was approved by the Second Affiliated Hospital of Zhejiang University School of Medicine Ethics Committee. Written informed consent was obtained from all participants.

2.2. Study population

WWE who used OXC while pregnant were eligible for inclusion. We searched patients from January 2017 to August 2023. Patients who began using OXC at least 6 months before conception and remained using it throughout the entire pregnancy were included in the study. Women receiving OXC mono-therapy or poly-therapy were both able to participate in the study. Patients were excluded if they had severe anemia, uncontrolled thyroid disease, progressive cerebral disease, renal or hepatic dysfunction, ethanol or illicit drug use, active suicidal ideation, or known poor ASMs adherence.

A significant reduction in the likehood of seizures recurring is shown in WWE who have been seizure-free for more than a year prior to conception [12,16]. Therefore, all the participants were divided into two groups: seizure-free group (defined as WWE who have been seizure-free for at least 12 months before conception) and non-seizure-free group (defined as WWE who have suffered from at least one seizure during the last 12 months before conception).

2.3. Data sources and measurements

OXC is rapidly absorbed and almost completely transformed into MHD [15]. In addition, exposure to OXC is negligibly small compared to MHD. Accordingly, we used high-performance liquid chromatography tandem-mass spectrometry (HPLC-MS/MS) to detect the sum of MHD and OXC amounts, in order to obtain the total serum OXC concentration for further calculation.

A baseline OXC concentration was detected in women who were planning to get pregnant. Patients were then followed up every 1–3 months at our epilepsy outpatient clinic. Blood samples for TDM were collected at each clinical visit throughout pregnancy. Samples were taken in a stable state of more than 5 days after the last dose adjustment and a fasting state before the morning dose. The attending neurologists assessed the management of seizures and the dosage of ASMs. OXC concentrations, concentrations of other ASMs, ASMs dosage, and seizure frequency changes were obtained from patient records.

2.4. Data analysis and statistical methods

The entire pregnancy period was split into three phases: the first trimester (<14 weeks GA), the second trimester (14–28 weeks GA), and the third trimester (>28 weeks GA-delivery). If multiple measurements were available for one given observation period, the average was derived.

Normally distributed continuous data were presented as mean ± standard deviation (SD). Continuous data that did not show a normal distribution were presented as median (interquartile range). Statistical analyses were all conducted with IBM SPSS (Version 26). All tests were two-sided, and $p < 0.05$ was considered statistically significant.

2.4.1. Concentration of OXC

The OXC concentration/dose (C/D) ratio was determined using the serum OXC concentrations (μg/ml) from routine TDM samples and the OXC dosage (g) from patient records. The C/D ratio was calculated for baseline before conception, as well as each trimester of all pregnancies. In absence of preconception OXC concentrations, non-pregnant baseline concentrations were assumed at least 4 weeks postpartum for 4 patients, which was a common practice in previous studies [2,17,18], as the pharmacokinetics and clearance of ASMs could quickly return to normal after birth [19]. Ratios of each trimester were compared to corresponding non-pregnant baseline C/D using the non-parametric testing of two independent samples (Mann-Whitney test).

The ratio of target concentration for OXC (RTC_OXC) was calculated by dividing the OXC concentration of a trimester (μg/ml) by the corresponding OXC concentration prior to pregnancy (μg/ml); thus, a value less than 1 denotes a decreased value compared to baseline concentration.

2.4.2. Seizure change

Based on the neurologists' notes in the patients' medical records, changes in seizure frequency were assessed throughout the three trimesters of pregnancy. Using univariate analysis and multivariate analysis of the logistic regression model, the association between age at conception, RTC_OXC, pregnancy period, ASMs and seizure changes were investigated. With a decrease or stabilization of 0, and an increase of 1, the changes in seizure frequency were considered as a binary variable. Age at conception was a continuous variable. Pregnancy period was an ordered categorization variable, with three trimesters defined as 1,2,3. Additionally, ASMs were also analyzed as binary variables, with mono-therapy recorded as 0 and poly-therapy recorded as 1.

2.4.3. RTC_OXC cut-off

To suggest a cut-off value for RTC_OXC, all patients' RTC_OXC data at all time points were pooled. Receiver Operating Characteristic (ROC) analysis was performed using seizure change value 1 as state variable. Test direction was set as: 'Smaller test result indicates a more positive actual state'. Optimal RTC_OXC cut-off value was defined as the value with the highest sum of sensitivity and specificity.

3. Results

3.1. Clinical characteristics of participants

Data on 25 pregnancies among 21 WWE were collected. Due to a lack of baseline OXC concentration or inability to adhere to regular medication concentration monitoring, nine pregnancies of 5 patients were excluded from the analysis. In the end, this study comprised 16 pregnancies of 16 WWE with an average age of 27.4 years old at the beginning of pregnancy. The flowchart of the study is presented in the supplement figure (Supplementary data 1).

Of the 16 pregnancies, nine obtained OXC mono-therapy, in the

remaining 7 pregnancies, either LEV (3), valproate (VPA) (1), LTG (1), LTG + perampanel (PER) (1), or LTG + topiramate (TPM) (1) were used in addition to OXC (Table 1). Supplement table 1 (Supplementary data 2) displays ASMs dosage adjustments during pregnancy.

3.2. OXC concentration during pregnancy

In the total group (Fig. 1A), the C/D ratio of OXC declined to 73.05 % in the first trimester when compared to the baseline, with a median of 11.16 (4.38) μg/ml/g versus 15.28 (4.37) μg/ml/g. It then dropped to 51.55 % in the second trimester [7.88 (3.20)] μg/ml/g and 62.18 % in the third trimester [9.50 (3.19)] μg/ml/g. Similar trends were seen in the non-seizure-free group and the seizure-free group (Fig. 1B).

The RTC_OXC was less than 0.8 in all trimesters of pregnancy in most cases. With medians less than 0.6, the second trimester had the lowest RTC_OXC values in the total group (Fig. 2A), the non-seizure-free group, and the seizure-free group (Fig. 2B).

3.3. Outcomes and determinants

While there was a clearly drop in OXC concentration during pregnancy (as measured by the C/D ratio and the RTC), increased seizure frequency was less common than decreased or stable seizure frequency (Fig. 3A, B, C). The second trimester of pregnancy was the time when seizure deterioration occurred the most (42.86 % in the total group, 37.50 % in the seizure-free group, and 45 % in the non-seizure-free group). Seizure frequency worsened in a higher percentage of the women in non-seizure-free group than in total group during the first trimester (36.36 % *vs* 26.67 %) and the second trimester (45 % *vs* 42.86 %). Seizures did not deteriorate in more than 40 % women in the seizure-free group at any time.

Table 1
Study population. ASMs, anti-seizure medications; CT, computerized tomography; EEG, electroencephalogram; LEV, levetiracetam; LTG, lamotrigine; MRI: magnetic resonance imaging; OXC, oxcarbazepine; PER, perampanel; TPM, topiramate; VPA, valproate.

	Total group	Non-seizure-free group	Seizure free group
Patients number, No.	16	11	5
Age at epilepsy onset, years	15.3 ± 7.1	15.5 ± 6.0	14.6 ± 9.8
Age at conception, years	27.4 ± 4.6	26.3 ± 4.6	29.8 ± 4.0
Duration of disease, years	12.1 ± 6.8	10.7 ± 4.2	15.2 ± 10.5
Residence, No.			
Urban	12	8	4
Rural	4	3	1
Education level, No.			
Illiteracy	1	1	0
Primary school	3	2	1
Middle school	6	5	1
University and above	6	3	3
Seizure type at epilepsy onset, No.			
Focal	10	7	3
Generalized	2	1	1
Combined generalized and focal	4	3	1
Etiology, No.			
Structural	4	3	1
Genetic/Metabolic	1	1	0
Infectious/Immune	2	1	1
Unknown	9	6	3
Abnormal cerebral MRI/CT findings, No.			
Yes	6	4	2
No	10	7	3
Epileptiform abnormalities on EEG at baseline, No.			
Yes	12	9	3
No	4	2	2
ASMs treatment during pregnancy, No.			
OXC monotherapy	9	5	4
OXC + LEV	3	2	1
OXC + VPA	1	1	0
OXC + LTG	1	1	0
OXC + LTG + PER	1	1	0
OXC + LTG + TPM	1	1	0

3.4. Factors associated with seizure change

Results of logistic regression analysis on seizures changes are presented in the supplement table 2 (Supplementary data 2). RTC_OXC was the only variable with statistical significance in the total group and the non-seizure-free group in both uni-variable analysis and multi-variable analysis, indicating that a higher RTC-value is associated with a decreased risk of seizure rise.

3.5. Threshold value of RTC

In the total group and the non-seizure-free group, RTC_OXC can help distinguish between patients at high risk and low risk for seizure deterioration. In the total group, the area under the ROC curve was estimated to be 0.729 (95 % CI: 0.592–0.866), and the RTC value with the highest sum of specificity and sensitivity was 0.575, with corresponding sensitivity and specificity values of 84.2 % and 63.9 % (Fig. 4A). In the non-seizure-free group, the area under the ROC curve was calculated to be 0.765 (95 % CI: 0.613–0.918). The optimal cut-off value for this group was also 0.575, with a sensitivity of 80.0 % and specificity of 70.8 % (Fig. 4B).

The theoretically optimal threshold value of 0.575 was compared to the commonly used value of 0.65 in the plot versus criterion analysis. RTC_OXC 0.65 was related to slightly higher sensitivity but substantially poorer specificity in both the total group as well as the non-seizure-free group (Fig. 4C, D).

4. Discussion

In this study, OXC concentration and seizure frequency variations in 16 WWE who received OXC during pregnancy in eastern China were retrospectively evaluated. OXC levels were observed to significantly decrease during pregnancy. The highest frequency of seizure deteriorating was observed to occur in the second trimester. Lower RTC_OXC was identified to be a risk factor for increasing seizure frequency. According to our knowledge, this is the first study that propose an RTC_OXC threshold of 0.575 for distinguishing WWE at high-risk and low-risk for seizure deteriorating during pregnancy.

Pregnancy-related physiological changes have an influence on ASMs absorption, distribution, metabolism, and excretion. These changes may lead to a decrease in serum ASMs concentrations, albeit the extent of decline differs across medications and individuals. According to our findings, OXC concentrations (whether measured by C/D ratio or RTC) started to decline in the first trimester and dropped more significantly in the second and third trimesters, which is consistent with previous studies [9,17,20]. For therapeutic practice, it is particularly important to understand the features of these concentration fluctuations. A prompt dose modification should be made to counteract the substantial drop in OXC concentration and reduce the risk of seizures.

Our study also contributes to the understanding of OXC pharmacokinetic alterations during pregnancy. OXC is mainly metabolized via glucuronidation [3], which may explain the similarity to LTG for the concentration changes during pregnancy [21]. Its main clinical active metabolite MHD is mostly eliminated through renal clearance. The pattern of OXC concentration fluctuations matches our knowledge of the way OXC clearance changes during pregnancy, with a peak clearance in the second trimester to 1.63- fold baseline and increased values persisted

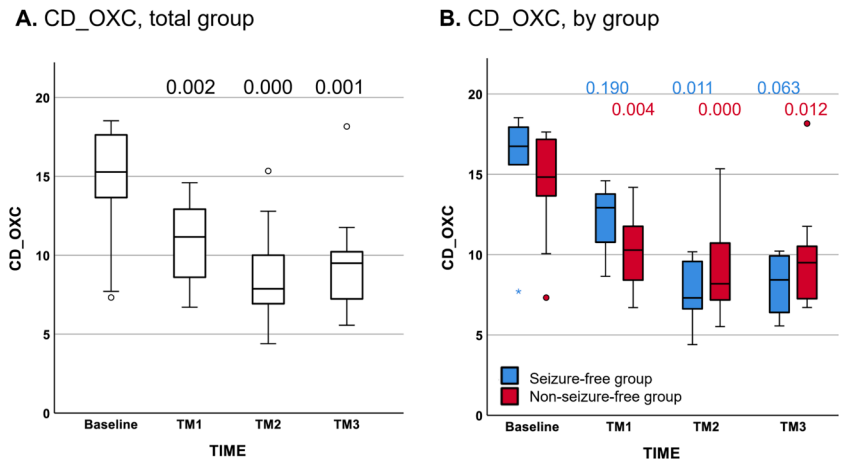

Fig. 1. Concentration/dose ratio of oxcarbazepine before and during pregnancy. A. Concentration/dose ratio of oxcarbazepine (CD_OXC) in the total group (n = 16). B. CD_OXC in the seizure-free group (n = 5, in blue) and the non-seizure-free group (n = 11, in red). The *p*-values represent comparisons with the corresponding baseline before conception. TM, trimester. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

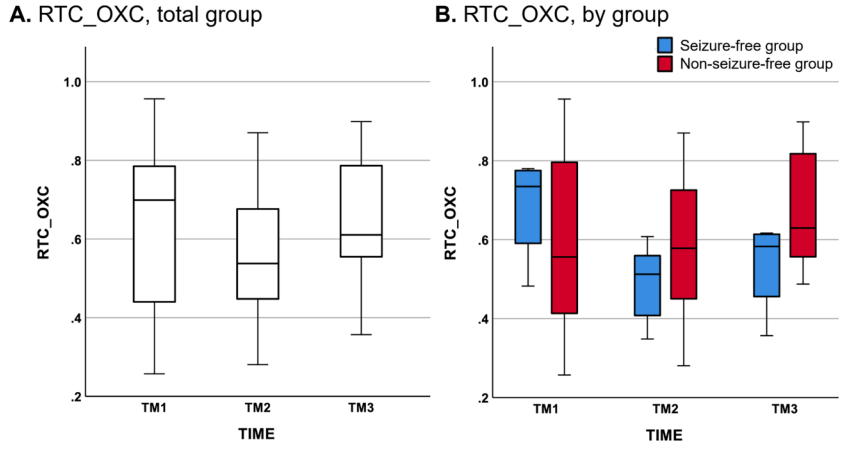

Fig. 2. The ratio of target concentration of oxcarbazepine during pregnancy. A. The ratio of target concentration of oxcarbazepine (RTC_OXC) in the total group (n = 16). B. RTC_OXC in the seizure-free group (n = 5, in blue) and the non-seizure-free group (n = 11, in red). TM, trimester. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

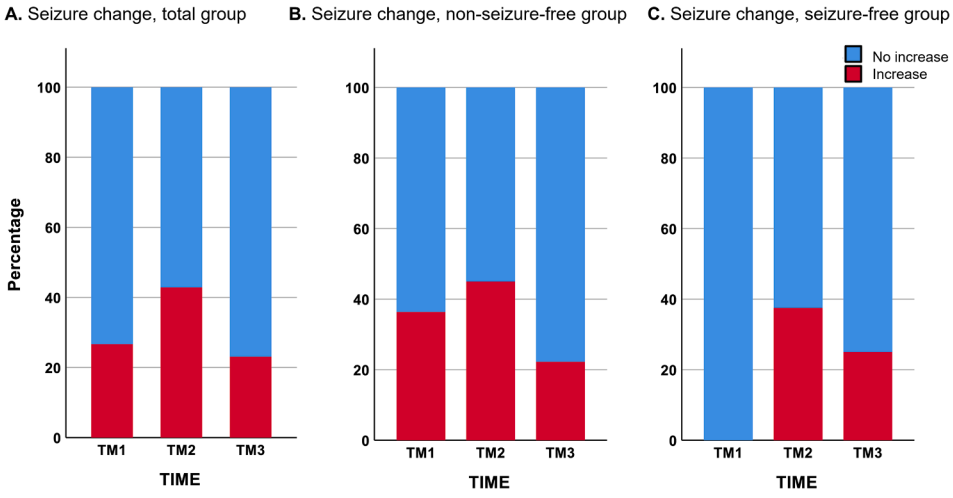

Fig. 3. Seizure change during pregnancy. Percentage of patients who suffered increased seizure frequency during pregnancy for (A) the total group, (B) the non-seizure-free group, and (C) the seizure-free group. TM, trimester.

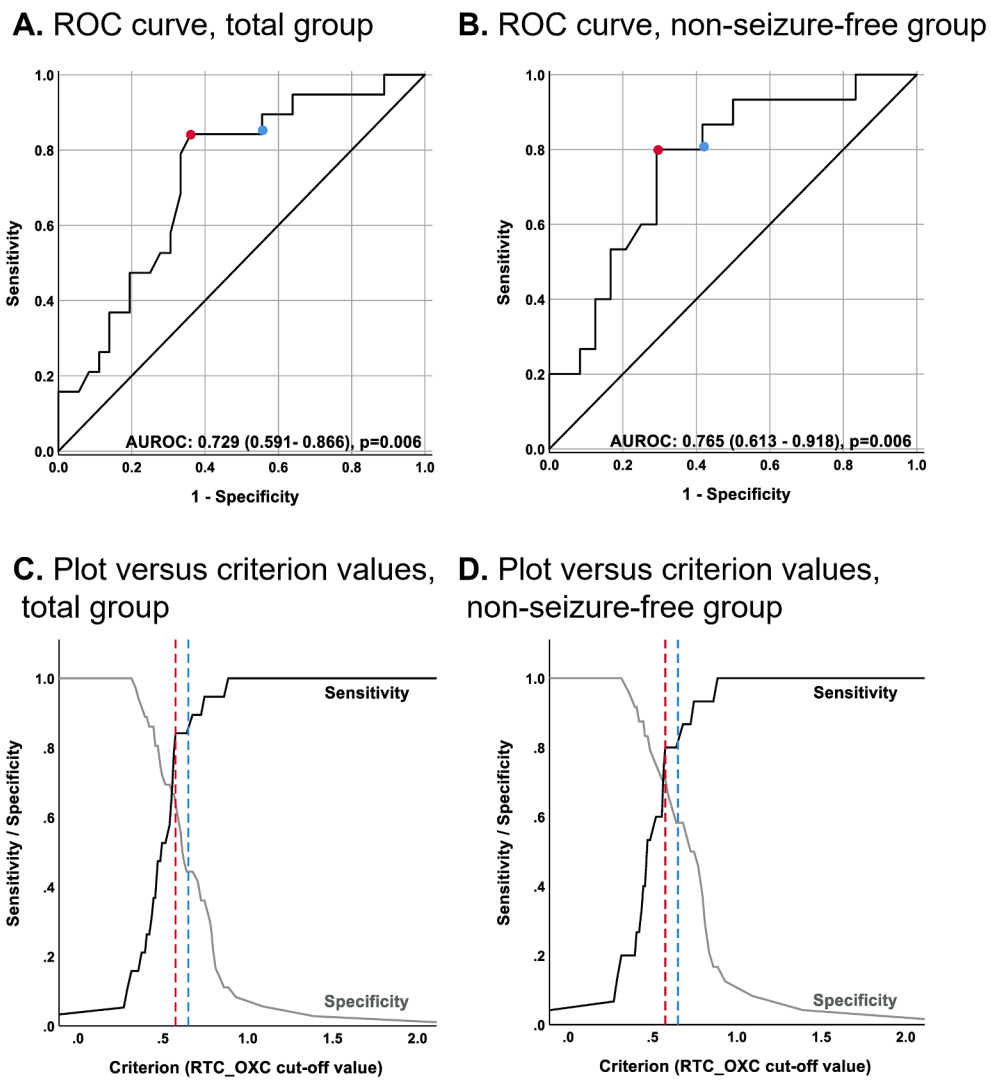

Fig. 4. Threshold values for ratio of target oxcarbazepine concentrations. (A) Receiver Operating Characteristic (ROC) curve for the total group, (B) ROC curve for the non-seizure-free group, (C) sensitivity/specificity *vs* criterion plot for the total group, (D) sensitivity/specificity *vs* criterion plot for the non-seizure-free group. Each curve shows 2 cut-off values: the most optimal value, which is derived by the highest sum of sensitivity and specificity (red), and the one that is clostest to 0.650 (blue). AUROC, the area under the receiver operating characteristic; RTC_OXC, the ratio of target concentration of oxcarbazepine. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in the third trimester (1.53- fold baseline)[2]. Although OXC concentration considerably decreased in all trimesters of pregnancy compared to the preconception baseline, this trend may have been underestimated due to dosage adjustments made by neurologists during TDM. When women of childbearing age express a desire to have children, our neurologists will adjust the ASMs regimen for WWE considering the teratogenicity of ASMs [22,23]. On the other hand, pregnancy-related poor concentration or increase in seizure frequency are likely to require an increase in OXC dosage. Several other scholars have noted this phenomenon and it is consistent with the clinical practice [6,24,25].

Our study highlights the value of preconception seizure management and counseling. The results of the epilepsy pregnancy registration study in Australia and the European Registry of Antiepileptic Drugs and Pregnancy (EURAP) both suggest that the duration of absence of seizures before pregnancy is a significant predictor of pregnancy seizures. A 74−92 % chance of being seizure-free during pregnancy existed for women who had no seizures within 9–12 months before pregnancy [25,26]. Taken all together, we suggest that women of childbearing age consult epilepsy specialists and obstetricians for ASMs adjustment and obstetric guidance before attempting to conceive, to achieve planned pregnancy as much as possible with epilepsy under control. Furthermore, it is recommended to test the serum OXC concentration before pregnancy, to establish a reference baseline for adjusting drug dosage during pregnancy.

As the pregnancy progresses into the second trimester, the risk of drug-induced teratogenicity decreases [5,27]. However, the blood concentration of OXC decreases, accompanied with insufficient sleep and increased stress, leading to an increased risk of seizures and obstetric complications [9,28]. GTCS are prone to serious adverse fetal events such as fetal arrest and miscarriage, and are also the leading cause of sudden unexpected death in epilepsy (SUDEP) in pregnant WWE [29]. Other seizures that impair the state of consciousness also pose significant potential risks. Therefore, avoiding seizures during pregnancy is the greatest safety guarantee for both the pregnant woman and the fetus.

It has been demonstrated that TDM during pregnancy improves seizure control. According to the American Academy of Neurology guidelines, LTG, carbamazepine, and phenytoin levels should be monitored during pregnancy, and that monitoring LEV and OXC levels should be take into consideration [30]. The data from the European and International Registry of Antiepileptic Drugs in Pregnancy pointed to the need for a more proactive approach to adjusting the dosages of all ASMs during pregnancy, particularly for pregnant women who experienced

seizures within the first trimester of their pregnancy [25]. In China, many neurologists and patients have not paid enough attention or had no option to conduct TDM during pregnancy, which has resulted in subpar epilepsy management or unfavorable pregnancy outcomes. In our study, although the dose of ASMs generally increased during the second and third trimester of pregnancy, it was accompanied by a decrease in OXC blood concentration, which further emphasizes the importance of TDM rather than empiric medication adjustment during pregnancy. We call on greater focus on pregnant WEE TDM, in order to enable more patients—particularly those with poorly controlled epilepsy—to receive close medication monitoring and epilepsy management. In situations where ASM concentration cannot be examined, drug dosage can be adjusted on evidence-based information and neurologists' experience.

In this study, we found a negative correlation between RTC_OXC and change in seizure frequency. To provide more information on this correlation we conducted an ROC analysis to identify which RTC threshold value best distinguishes between patients who are at high risk for seizure worsening and patients who are not. For both the total group and the non-seizure-free group, this analysis revealed an optimal cut-off value of 0.575, which has the highest sum of sensitivity and specificity. While the specificity of 63.9 % in the total group and a slightly higher specificity of 70.8 % in the non-seizure-free group was not great, this could be partly due to insufficient sample size in the analysis. The same issue arises in similar investigations [11,12]. Future multi-center, large-sample studies are needed to make up for this shortcoming. Although relatively limited monitoring data is insufficient to obtain targeted threshold for the seizure-free group, we still recommend TDM for these patients because OXC concentrations significantly decrease during their pregnancies.

According to a retrospective chart review study, seizures worsened for all ASMs when concentrations dropped below 65 % of the preconception baseline [16,31]. Another prospective study also supported the clinical relevance of RTC < 0.65 as a critical threshold [10]. For this reason, we compared RTC_OXC 0.575 with the commonly used value of RTC_OXC 0.65, and found that the latter was related to slightly higher sensitivity but substantially poorer specificity in both the total group as well as the non-seizure-free group, which will thus generate many false positives. Therefore, we recommend that RTC_OXC 0.575 is a suitable cut-off value to assist identify the risk of seizure deterioration during pregnancy in WWE, and we suggest maintaining OXC concentrations greater than 57.5 % of preconception levels.

This study is limited by the retrospective nature and the relatively small sample size, yet it provides clinically relevant findings that require confirmation in further large prospective cohort study. A more thorough assessment of the relationship between OXC concentration and seizure control during pregnancy is in need, at narrower time intervals and ideally take into account additional factors that can affect seizure frequency, such as stress, sleep deprivation, hormone and neuroactive steroid concentrations, OXC poly-therapy with different additional ASMs. The inability to determine ASMs adherence is another restriction. In the meantime, selection bias of epilepsy patients in tertiary hospitals as well as recall bias about seizures during pregnancy may have occurred.

In conclusion, this study demonstrated a substantial decrease in OXC concentration during pregnancy in eastern China WWE. The second trimester of pregnancy was also the time when seizure deterioration occurred the most, especially for patients with poor seizure control before pregnancy. For all pregnant WWE, lower OXC RTC was a significant predictor of seizure deterioration, and we suggest neurologists to maintain OXC concentrations greater than 57.5 % of preconception levels.

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Disclosures

The authors report no relevant disclosures.

Ethical statement

This study was approved by the Second Affiliated Hospital of Zhejiang University School of Medicine Ethics Committee. The work described in this study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The manuscript is in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journal.

We certify that this manuscript is original and has not been published and will not be submitted elsewhere for publication while being considered by *Epilepsy & Behavior Reports*. And the study is not split up into several parts to increase the quantity of submissions and submitted to various journals or to one journal over time. No data have been fabricated or manipulated (including images) to support the conclusions. No data, text, or theories by others are presented as if they were our own.

The submission has been received explicitly from all co-authors. And authors whose names appear on the submission have contributed sufficiently to the scientific work and therefore share collective responsibility and accountability for the results.

CRediT authorship contribution statement

Lin-yan Wei: Writing – original draft, Visualization, Methodology, Investigation, Data curation. **Zheng-yan-ran Xu:** Writing – review & editing, Validation, Methodology, Investigation, Data curation. **Zhen-zhen Lai:** Writing – review & editing, Resources, Methodology. **Na Dong:** Writing – review & editing, Resources, Methodology. **Yi-wen Sang:** Writing – review & editing, Resources, Methodology. **Yi Guo:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebr.2023.100640.

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