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Clinical characteristics and pregnancy outcomes of new onset epilepsy during pregnancy

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Abstract

The occurrence of seizures during pregnancy is really a challenging situation which risks the health of both mothers and fetuses. However, new onset epilepsy is unpredictable in pregnancy, and its clinic feature is barely known. This study aimed to explore the clinical characteristics and pregnancy outcomes of new onset epilepsy during pregnancy.

We screened consecutive women with epilepsy and reproductive history from June 2013 to November 2018 from 3 hospitals in West China. Detailed demographics, clinical features, neurological status, related tests, managements, seizure and pregnancy outcomes were recorded and followed-up. Within them, patients with first seizure during pregnancy and spontaneous recurrent seizures after delivery or abortion were defined as new onset epilepsy during pregnancy.

We screened a total of 1041 consecutive women with epilepsy and reproductive history. Twenty-two of them (2.1%) had new onset epilepsy during pregnancy. The average age at seizure onset was 22.7 ± 3.0 years. All their first seizures occurred in pregnancy period, including 4 (18.2%) in the first trimester, ten (45.4%) in the second trimester and eight (36.4%) in the third trimester. Most patients delivered healthy babies, except one patient had to choose induced abortion because of the disappearance of fetal heart rate, one child was diagnosed with mild harelip and one was diagnosed with trisomy 21 syndrome, tetralogy of Fallot and congenital duodenal atresia. All 3 complications happened in patients with their first seizures in first trimester.

Although the risk of new onset epilepsy during pregnancy was relatively low, accurate diagnosis and appropriate treatment were required to reduce the damage to both mothers and fetuses. New onset epilepsy during pregnancy mostly began in middle and late pregnancy. However, seizures occurred from early pregnancy had bad effects on the embryo or fetus.

Abbreviations: ILAE = International League Against Epilepsy; SD = standard deviations; GTCS = generalized tonic-clonic seizures; sGTCS = secondary generalized tonic-clonic seizures; FS = focal seizures; CSE = convulsive status epilepticus; AED = antiepileptic drug; WWE = women with epilepsy; LEV = Levetiracetam; PHT = phenytoin; CBZ = carbamazepine; HS = hippocampus sclerosis; FCD = focal cortical dysplasia.

Keywords: epilepsy, new onset, outcomes, pregnancy, seizure

1. Introduction

Epilepsy is one of the common chronic disorders affecting women of reproductive age.[1] The occurrence of seizures during pregnancy is really a challenging situation which risks the health of both mothers and fetuses.[2] Lots of evidences indicate that seizures in pregnancy are related to miscarriage, stillbirth, preterm delivery, antepartum and post-partum bleeding, caesarean section, developmental delay and congenital malformation.[1–3] Seizures in pregnancy mainly result from 3 conditions: first and most frequent is uncontrolled pre-existing seizures; second is the new onset seizures; and third is some pregnancy-related conditions, especially the eclampsia.[4] Women with pre-existing epilepsy can plan their pregnancies after controlling seizures and consulting doctors. Women with risk of eclampsia may have some evidences of preeclampsia which can be regularly monitored and prevented in advance. However, new onset seizures are unpredictable in pregnancy, which need extremely accurate diagnosis and appropriate treatment.

Previous studies showed that structural and metabolic changes may precipitate new onset seizures during pregnancy, including intracranial hemorrhage, cerebral venous sinus thrombosis, ischemic stroke, brain tumor, hydrocephalus, infection, hypoglycemia, acute intermittent porphyria, and so on.[5,6] However, most of these seizures were only the acute symptoms of underlying diseases; rare would develop into epilepsy, especially without obvious structural abnormalities. There is a condition that some women may have their first seizures during pregnancy and continue to get spontaneous recurrent seizures after delivery, which is called new onset epilepsy during pregnancy.[7]

Up to now, the characteristics of new onset epilepsy during pregnancy and its effect to both mothers and fetuses are barely known. Here, we investigated the clinical features, managements and pregnancy outcomes of a series of patients with new onset epilepsy during pregnancy from West China. To our knowledge,

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this is the first comprehensive assessment of new onset epilepsy during pregnancy, with a relatively large cohort of patients.

2. Methods

2.1. Patients and registrations

Patients were selected from West China Pregnancy Register for epilepsy patients. Women with epilepsy and reproductive history were consecutively registered and followed up from June 2013 to November 2018. We collected patients from 3 hospitals in West China, including 2 general hospitals (West China Hospital, Sichuan Provincial People's Hospital) and one specialist women and children's hospital (West China Second Hospital). All patients were diagnosed with epilepsy according to the 2010 International League Against Epilepsy (ILAE) Classification Schemes of Epileptic Seizures and Epilepsy Syndromes.[8] Generalized seizures are defined as seizures occurring in and rapidly engaging bilaterally distributed networks. Generalized tonic-clonic seizure (GTCS) is the common type of generalized seizures. Patients with GTCS will quickly lose consciousness and their skeletal muscles will suddenly tense, often causing a fall. A few seconds later, the patient's muscles start to contract and relax rapidly, causing convulsions. And focal seizures (FS) are defined as seizures occurring within networks limited to one hemisphere and either discretely localized or more widely distributed. Symptoms vary according to where the seizures occur, including asymmetrical tonic or excessive exercise from the frontal lobe, the feeling of déjà vu or automatism from the temporal lobe, the numbness or tingling from the parietal lobe, the visual disturbance or hallucination from the occipital lobe, etc. Furthermore, convulsive status epilepticus (CSE) is characterized either by continuous bilateral convulsive activity (lasting more than five minutes) or by generalized convulsive seizures that recur without significant recovery between them. Detailed demographics, clinical features, neurological status, related tests, managements, seizure and pregnancy outcomes were recorded. Women would be followed up at the clinic or by telephone every 3 months before delivery and every year after delivery. Their seizure outcomes and the condition of their babies would be collected and recorded. Seizure frequency in pregnancy was fixed for each trimester and was categorized as no seizures, sporadic seizures (less than one seizure per month), frequent seizures (more than one seizure per month) and very frequent seizures (more than one seizure per week).

Within them, patients with new onset epilepsy during pregnancy were recruited into our final analysis. The inclusion criteria were as follows:

1. women with first seizure during pregnancy;
2. women with spontaneous recurrent seizures after delivery.[7]

The exclusion criteria were as follows:

1. women with first seizure before pregnancy;
2. women with first seizure after delivery;
3. women with evidence of eclampsia;
4. women with other severe neurological, psychiatric or systemic diseases.

The study was approved by the ethics committee of West China Hospital, Sichuan University and we confirmed that all methods were performed in accordance with the relevant guidelines and regulations. Informed consents were obtained from all participants.

2.2. Statistical analysis

Statistical analysis was performed using SPSS (version 20.0, SPSS Inc., Chicago, IL). Descriptive analysis was applied to deal with the demographics, clinical features and pregnancy outcomes, showing as percentages, means, and standard deviations (SD). Table 1

3. Results

3.1. Clinical features

We screened a total of 1041 consecutive women with epilepsy and reproductive history from June 2013 to June 2018. Twenty-two of them (2.3%) reached the standard of new onset epilepsy during pregnancy and were finally included into this study. The sociodemographic and clinical characteristics of these 22 patients were showed in Table 2. The average age at seizure onset was 22.7 ± 3.0 years (range: 19–28 years). All their first seizures occurred in the pregnancy period, including 4 (18.2%) in the first trimester, 10 (45.4%) in the second trimester and 8 (36.4%) in the third trimester. Most patients (13/22, 59.1%) suffered primary or secondary GTCS in pregnancy, while 7 (31.8%) suffered FS. Furthermore, 2 patients (9.1%) only suffered CSE in the third trimester. As for the seizure frequencies of other 20 patients without CSE, sporadic seizures were found in most patients (16/22, 71.7%), while frequent seizures and very frequent seizures were only found in 2 patients respectively.

3.2. Related examinations

Routine antenatal examinations were performed in almost all patients, including physical examination, laboratory tests and prenatal ultrasounds. There was no evidence of preeclampsia, including hypertension, proteinuria, thrombocytopenia or dysfunction of liver and kidney. Chromosome test was performed in 18 patients (81.8%) and obvious abnormality (trisomy 21 syndrome) was found in 1 fetus. Besides, congenital heart disease (tetralogy of Fallot) was also detected in the same fetus. The mother suffered her first seizure in first trimester and insisted to deliver the baby because of her religion for not killing.

3.3. Treatment and outcome

Folate (0.4 mg/day) was supplemented throughout the first trimester in 11 patients (50%). Fourteen patients were diagnosed with epilepsy during pregnancy and were advised to begin antiepileptic drug (AED) therapy, while only 8 of them took the AED (levetiracetam in 4, carbamazepine in 1, phenytoin in 1 and intravenous diazepam in 2 CSE) in pregnancy. The other 6 chose to start the AED after delivery because of worrying about the teratogenic effect of AED. Moreover, the other 8 patients were diagnosed with epilepsy and began AED therapy after delivery or abortion. All patients suffered similar unprovoked seizures after delivery (21/22, 95.5%) or abortion (1/22, 4.5%) because of bad response to initial AED or inappropriate AED withdrawal.

Most patients (16/22, 72.7%) had easy deliveries and gave birth to healthy babies, while 6 of them (27.3%) faced abnormal situations. Three babies suffered fetal distress before delivery and had to get treatment in neonatology department, fortunately, without severe complications. Two of them happened in patients with CSE in third trimester. However, the other 3 were much worse. One patient had to choose induced abortion in first

Table 1

Sociodemographic and clinical characteristics of patients with new onset epilepsy during pregnancy.

Variable	Number	Proportion	Mean	SD	Range
Female	22	100%	–	–	–
Education years					
<9	1	4.5%	–	–	–
9–12	14	63.6%	–	–	–
>12	7	31.8%	–	–	–
Previous pregnancy					
0	14	63.6%	–	–	–
1	7	31.8%	–	–	–
2	1	4.5%	–	–	
Age at seizure onset (yr)	–	–	22.7	3.0	19-28
Seizure type					
FS	7	31.8%	–	–	–
GTCS	10	45.5%	–	–	–
sGTCS	3	13.6%	–	–	–
CSE	2	9.1%	–	–	–
Seizure frequency in pregnancy					
Sporadic	16	71.7%	–	–	–
Frequent	2	9.1%	–	–	–
Very frequent	2	9.1%	–	–	–
CSE	2	9.1%	–	–	–
Pregnancy period of first seizure					
First trimester	4	18.2%	–	–	–
Second trimester	10	45.4%	–	–	–
Third trimester	8	36.4%	–	–	–
AED during pregnancy					
LEV	4	18.2%	–	–	–
CBZ	1	4.5%	–	–	–
PHT	1	4.5%	–	–	–
DIA (iv)	2	9.1%	–	–	–
Folate supplement (0.4mg/d)	11	50%	–	–	–
Neuroimaging finding					
Negative	19	86.4%	–	–	–
Positive			–	–	–
HS	1	4.5%	–	–	–
Possible FCD	2	9.1%	–	–	–
Abnormal situation in pregnancy					
Fetal distress	3	13.6%	–	–	–
Induced abortion	1	4.5%	–	–	–
Mild harelip	1	4.5%	–	–	–
Trisomy-21 syndrome	1	4.5%	–	–	–

SD = standard deviation; FS = focal seizures; GTCS = generalized tonic-clonic seizures; sGTCS = secondary generalized tonic-clonic seizures; CSE = convulsive status epilepticus; AED = antiepileptic drug; LEV = levetiracetam; CBZ = carbamazepine; PHT = phenytoin; DIA (iv) = diazepam (intravenous); HS = hippocampus sclerosis; FCD = focal cortical dysplasia.

trimester because of the disappearance of fetal heart rate. One baby was diagnosed with mild harelip. And 1 was diagnosed with trisomy-21 syndrome, tetralogy of Fallot and congenital duodenal atresia. All the 3 serious complications happened in patients with first seizure in first trimester. Detailed clinical information of each patient was showed in Table 2.

4. Discussion

Seizures in pregnancy risk the health of both mothers and fetuses. Previous studies mostly focused on uncontrolled pre-existing epilepsy or provoked seizures during pregnancy, while rare focused on the new onset epilepsy.[4] New onset epilepsy during pregnancy was a challenging and long-term problem affecting patients before and after delivery. Thus, accurate diagnosis and appropriate treatment were of great importance. In this study, we reviewed the features and pregnancy outcomes of patients with new onset epilepsy during pregnancy, which was barely explored before.

Up to now, little had been known about the accurate incidence of new onset epilepsy during pregnancy. This present study showed a relatively low risk of new onset epilepsy during pregnancy in our Pregnancy Register for epilepsy patients (22/1041, 2.1%). It was similar to the proportion of gestational onset focal epilepsy (FE) (4/116, 3.4%) reported by Yakunina et al.[9] However, in another study from Azerbaijan, the proportion was much higher (10.5%).[10] They prospectively recruited 105 pregnant women with epilepsy (WWE) and found 11 women with their first seizures during the current pregnancy. Different populations and inclusion criteria may be the reason. Besides, it was difficult to confirm whether the 11 patients got spontaneous recurrent seizures after delivery or it was just acute symptom of pregnancy-related condition, especially the eclampsia.

In our 22 patients, mean age at seizure onset was 22.7 ± 3.0 years (range: 19–28 years), which was in the favorable reproductive stage and indicated that age might not be the risk factor for new onset epilepsy during pregnancy. However, the pregnancy period of their first seizures was different, including 4 (18.2%) in the first trimester, 10 (45.4%) in the second trimester and 8 (36.4%) in the third trimester. It seemed that new onset epilepsy during pregnancy preferred to occur in the middle and late pregnancy (18/22, 81.8%), which might reduce the bad effect on fetus. It was proved by our finding that all 3 bad complications (induced abortion because of the disappearance of fetal heart rate; trisomy-21 syndrome, tetralogy of Fallot and congenital duodenal atresia; mild harelip) occurred in patients with their first seizure in first trimester. As the key development period of embryo or fetus, any abnormal conditions in first trimester would become vital risks, especially one or more seizures. By contrast, although 2 patients experienced CSE and 3 fetuses suffered fetal distress in third trimester, no obvious complications occurred in mothers or babies.

As for the seizure type in pregnancy, other studies about pre-existing epilepsy showed that generalized epilepsy was more common than focal epilepsy.[11,12] It was in keeping with our findings that most patients (59.1%) suffered primary or secondary GTCS in pregnancy. Furthermore, CSE was observed in 2 patients (2/22, 9.1%) in third trimester, which was more common than that of pre-existing epilepsy. It was reported that only 1% to 2% of women with pre-existing epilepsy may experience CSE in pregnancy.[11] Although CSE during pregnancy was associated with high morbidity and mortality, timely and appropriate treatment could lead to a satisfying result. Besides, most patients (16/22, 71.7%) only suffered sporadic seizures (less than 1 seizure per month) during pregnancy. The new onset seizures in pregnancy seemed to be either mild or serious.

In addition to new onset seizures, AED was another problem that patients with new onset epilepsy during pregnancy had to face. To avoid the maternal and fetal risk associated with seizures, AED therapy was often maintained during pregnancy, despite increasing the risk of congenital malformation and adverse cognitive development in babies.[13] In this study, only 8 patients started their AED therapies during pregnancy (1 from the first trimester, 4 from the second trimester, 3 from the third trimester). Levetiracetam (LEV) was the most favorable drug, prescribed to 4 patients (50%). Only 1 patient with LEV (1 g/d) and sporadic focal seizure from first trimester delivered a baby

Table 2

Detailed clinical information of each patient with new onset epilepsy during pregnancy.

Patient	Age at seizure onset	Period of first seizure	Seizure type	Seizure frequency	AED in pregnancy	Abnormality in pregnancy	Abnormality during delivery	Infant malformation	MRI/CT finding
1	25	first trimester	GTCS	sporadic	none	none	none	none	negative
2	25	first trimester	GTCS	sporadic	none	fetal heart rate disappeared	induced abortion	NA	negative
3	27	first trimester	FS	sporadic	LEV 1 g/d	trisomy-21 syndrome, tetralogy of Fallot	none	trisomy-21 syndrome, tetralogy of Fallot, congenital duodenal atresia	negative
4	23	first trimester	sGTCS	sporadic	none	none	none	mild harelip	negative
5	21	second trimester	FS	sporadic	PHT 0.2 g/d	none	none	none	HS
6	28	second trimester	GTCS	sporadic	none	none	none	none	negative
7	20	second trimester	GTCS	sporadic	none	none	none	none	negative
8	20	second trimester	GTCS	frequent	CBZ 0.1 g/d	none	none	none	negative
9	22	second trimester	FS	sporadic	none	none	none	none	negative
10	26	second trimester	sGTCS	sporadic	none	none	none	none	negative
11	23	second trimester	FS	sporadic	LEV 0.5 g/d	none	none	none	negative
12	22	second trimester	sGTCS	frequent	LEV 0.5 g/d	none	none	none	negative
13	19	second trimester	GTCS	sporadic	none	none	none	none	negative
14	20	second trimester	GTCS	sporadic	none	none	none	none	negative
15	25	third trimester	GTCS	sporadic	LEV 0.5 g/d	none	none	none	negative
16	21	third trimester	CSE	CSE	DIA (iv)	none	fetal distress	none	negative
17	20	third trimester	GTCS	very frequent	none	none	none	none	negative
18	20	third trimester	GTCS	sporadic	none	none	fetal distress	none	negative
19	19	third trimester	FS	sporadic	none	none	none	none	negative
20	20	third trimester	CSE	CSE	DIA (iv)	none	fetal distress	none	possible FCD
21	27	third trimester	FS	very frequent	none	none	none	none	possible FCD
22	27	third trimester	FS	sporadic	none	none	none	none	negative

GTCS = generalized tonic-clonic seizures; sGTCS = secondary generalized tonic-clonic seizures; FS = focal seizures; CSE = convulsive status epilepticus; AED = antiepileptic drug; LEV = levetiracetam; PHT = phenytoin; CBZ = carbamazepine; DIA (iv) = intravenous diazepam; NA = not applicable; HS = hippocampus sclerosis; FCD = focal cortical dysplasia.

with major congenital malformation (trisomy-21 syndrome, tetralogy of Fallot and congenital duodenal atresia).

Structural and metabolic changes were regarded to precipitate new onset seizures during pregnancy.[5,6,10] Most provoked seizures, however, could not be diagnosed as epilepsy, except spontaneous recurrent seizures occurred. In this study, 3 positive neuroimaging findings were detected from brain MRI images (3/22, 13.6%), including hippocampus sclerosis (HS) in 1 patient and possible focal cortical dysplasia (FCD) in 2 patients. This was different from usual gestational cerebral complications, such as cerebral venous sinus thrombosis, intracranial hemorrhage and ischemic stroke. Furthermore, eclampsia, the most common disease needed to be distinguished in pregnancy, was defined as the onset of generalized seizures that could not be attributed to other causes in pregnant women with pre-eclampsia.[14] And pre-eclampsia was traditionally diagnosed by the de-novo hypertension combined with proteinuria, while in the new definition, with other maternal organ dysfunctions, such as renal insufficiency, liver involvement, neurological or haematological complications, uteroplacental dysfunction, or fetal growth restriction.[15,16] These signs were regularly examined in pregnancy and were used to exclude patients with eclampsia in our study. Moreover, there was barely evidence that patients with eclampsia could develop into chronic epilepsy after delivery.

5. Limitations

The current study had several limitations that needed to be addressed. First, since the incidence of new onset epilepsy during pregnancy was relatively low, the sample size was small, which may limit the power of our findings for clinical applications. Second, some information during pregnancy were retrospectively collected in some cases, which may contain some recall bias. We attempted to minimize the bias by verifying the information through examining corresponding medical records as much as possible. Third, our pregnancy register was conducted in one province, thus some selection bias seemed to be inevitable. However, our patients were selected from 3 general hospitals, which increased the representativeness of our population. More prospective, population-based and nationwide data are needed in the future studies.

6. Conclusion

Although the risk of new onset epilepsy during pregnancy was relatively low, accurate diagnosis and appropriate treatment were required to reduce the damage to both mothers and fetuses. New onset epilepsy during pregnancy mostly began in middle and late pregnancy. However, seizures occurred from early pregnancy had bad effects on the embryo or fetus. Furthermore, the risk of convulsive status epilepticus seemed high in patients with new onset epilepsy during pregnancy.

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References

[1] Viale L, Allotey J, Cheong-See F, et al. Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis. Lancet 2015;386:1845–52.
[2] Shuster EA. Seizures in pregnancy. Emerg Med Clin North Am 1994;12:1013–25.
[3] Yerby MS. Pregnancy, teratogenesis, and epilepsy. Neurol Clin 1994;12:749–71.
[4] Aya AG, Ondze B, Ripart J, et al. Seizures in the peripartum period: Epidemiology, diagnosis and management. Anaesth Crit Care Pain Med 2016;35:S13–21.
[5] Robert LB, Peter WK. Seizures in pregnancy: diagnosis and management. Int Rev Neurobiol 2008;83:259–71.
[6] Van Loenena NTVM, Hintzenb RQ, de Groota CJM. New onset seizures in pregnancy caused by an unexpected neurologic disorder. Eur J Obstet Gynecol Reprod Biol 2004;117:109–11.
[7] Thomas SV. Management of epilepsy and pregnancy. J Postgrad Med 2006;52:57–64.
[8] Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia 2010;51:676–85.
[9] Yakunina AV, Poverennova IE, Veldiaksova ED. The peculiarities of the focal epilepsy during pregnancy and after childbirth. Sib Med Rev 2017;1:63–9.
[10] Shahla M, Hijran B, Sharif M. The course of epilepsy and seizure control in pregnant women. Acta Neurol Belg 2018;118:459–64.
[11] EURAP Study GroupSeizure control and treatment in pregnancy: observations from the EURAP epilepsy pregnancy registry. Neurology 2006;66:354–60.
[12] Thomas SV, Syam U, Devy JS. Predictors of seizures during pregnancy in women with epilepsy. Epilepsia 2012;53:85–8.
[13] Razaz N, Tomson T, Wikström AK, et al. Association between pregnancy and perinatal outcomes among women with epilepsy. JAMA Neurol 2017;74:983–891.
[14] ACOG. Diagnosis and management of preeclampsia and eclampsia. ACOG practical bulletin. Clinical management guidelines for obstetrician-gynecologists. 2002. Obstet Gynecol. 2002:99:159-166.
[15] Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. BMJ 2013;347:f6564.
[16] Mol BWJ, Roberts CT, Thangaratinam S, et al. Pre-eclampsia. Lancet 2016;387:999–1011.