Original Article

Assessing Antiepileptic Drugs in Women with Epilepsy during Pregnancy in Srinagarind Hospital, Khon Kaen University, Thailand

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Background: Epilepsy in pregnant women was related with many complications by itself. Antiepileptic drugs were prescribed for decreasing the frequent and severity of seizure, they causes malformation in the fetus.

Objective: To assessing antiepileptic drugs in women with epilepsy during pregnancy in Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand. The second objective was to review abnormal congenital malformation effect of antiepileptic drugs, specialty in type of drug used in the hospital.

Materials and Methods: A retrospective study was conducted in all pregnant women who using antiepileptic drugs during 2015 to 2019. Review the literature were searched from online publishing report.

Results: The preliminary data from the hospital showed 7 AEDs used in pregnant period. The AEDs which highly used including phenobarbital, levetiracetam, and valproic acid, respectively. Co-medication was folic acid, ranitidine, and multivitamin. The review literation data showed valproic acid or valproate was the high risk drug inducing of congenital malformation in children who received AEDs during grown in uterus. The major congenital malformation composed of orofacial clefts, neural tube defects, and limb deficiencies, and usually found in older AEDs than new drug group.

Conclusion: AEDs or epilepsy causes increases the risk of many complications in both maternal and child. It is challenging to obstetricians, neurologist, and pediatric doctors for well co-operation to management of WWE who intake AEDs during pregnant for good outcomes of maternal and her child at post-partum period.

Keywords: Women with epilepsy (WWE), Pregnancy, Antiepileptic drugs, Epilepsy clinic Srinagarind hospital

J Med Assoc Thai 2021;104(Suppl.1): S77-80
Website: http://www.jmatonline.com

Epilepsy defined as the presence of recurrent, unprovoked seizure. It is the most common chronic neurological condition, affects 0.6 to 1% of the population[1]. Antiepileptic drugs (AEDs) are the typical therapy of this disease, daily intake with long term period. Epilepsy women become pregnant or pregnant women has seizure, all of them were leading frequent seizures, increasing the risk of pregnancy-related complication[2,3]. The fetus in uterus can received AEDs because it can be transferred via the placenta[2] 4 to 8% of pregnant women taking AEDs chance of giving a child with a major congenital malformation (MCM[2-4], and 2 to 3 fold increased risk of CM compared to the general population[5]. In the year 1960s, the first report of teratogenicity effect of AEDs from an exposure during pregnancy[6]. There are many study compared the safety of AEDs, including of old and news AEDs, dosage of each drugs, monotherapy and polytherapy. The researcher showed some AEDs such as valproic acid and phenobarbital were associated with a higher risk of major malformations than newer AEDs (lamotrigine and levetiracetam). But some new AEDs such as topiramate was associated with an increased risk of CM compared with a general population[7]. In addition, the data of carbamazepine in highest dosage showed a significantly increases the prevalence of major congenital malformations and cognitive impairment[8-11]. Congenital monitoring process were performed in 42 country in Europe, Australia, and Asia, EURAP-The European Registry of Antiepileptic drugs and Pregnancy, pregnant women who using AEDs for long term treatment of epilepsy or other problem such as trigeminal neuralgia, bipolar, neuropathic pain. They have to registry started at during child bearing until 1 year postpartum period[7]. The primary objective of this study was to assessing antiepileptic drugs in women with epilepsy during pregnancy in Srinagarind hospital, Faculty of Medicine, Khon Kaen University, Thailand. The

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How to cite this article:
Chainirun N, Tiamkao S, Phunikhom K. Assessing Antiepileptic Drugs in Women with Epilepsy during Pregnancy in Srinagarind Hospital, Khon Kaen University, Thailand. J Med Assoc Thai 2021;104 (Suppl.1): S77-80.
doi.org/10.35755/jmedassocthai.2021.S01.12280

second objective was to review abnormal congenital malformation effect of antiepileptic drugs, specialty in type of drug used in the hospital.

Materials and Methods

A retrospective study was conducted in all pregnant women who using antiepileptic drugs during 2015 to 2019. Review the literature were searched from online publishing report. The study protocol was approved by the EC (HE631638).

Results

The prevalence of congenital malformation showed in the Table 1. The data was showed that valproic acid was the high risk drug inducing of congenital malformation in children who received AEDs during grown in uterus, and any AEDs were phenytoin, lamotrigine, carbamazepine, and phenobarbital, respectively. The major congenital malformation composed of orofacial clefts, neural tube defects, and limb deficiencies, and usually found in older AEDs than new drug group.

The preliminary data from the hospital showed 7 AEDs used in pregnant period. The AEDs which highly used including phenobarbital, levetiracetam, and valproic acid, respectively. Maternal age was 22 to 30 years-old. Co-medication was folic acid, ranitidine, and multivitamin. The data was showed in Table 2.

Discussion

The review literature reported[3-17], there are many

Table 1. The risk of major and minor congenital malformations with monotherapy used of AED

AED	Risk in percentage (%)	Congenital malformation
Valproic acid	6.2 to 20.3	Spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly, craniosynostosis, neural tube defects, cognitive impairment
Phenobarbital	4.9 to 6.5	Craniofacial, digital abnormalities, cleft lip, cleft palate cloacal anomaly, cardiac malformations, cognitive impairment
Phenytoin	2.9 to 11	Microcephaly, nail hypoplasia, facial clefts ,congenital heart disease, cognitive impairment
Carbamazepine	2.2 to 5.5	Spina bifida, cardiac malformations, hypospadias, orofacial clefts
Topiramate	3.9 to 4.8	Cleft lip with/without cleft palate, hypospadias
Lamotrigine	3.2 to 10.4	Clubfoot, orofacial clefts, cardiac malformations, hypospadias, neural tube defects
Levetiracetam	2.03 to 2.8	Cardiac malformations , neural tube defects
Gabapentin	3.2	Cardiac malformations, small for gestational age (SGA), preterm birth (PTB), neonatal intensive care unit admission (NICUa)
Oxcarbazepine	3	Cardiovascular defects

Table 2. Demographic data of AEDs used in pregnant women at Srinagarind hospital, Faculty of Medicine, Khon Kean University, Thailand

Year	Patient (n)	Mean age ± SD (range)	AEDs	Co-medication
2015	1	30	Phenobarbital (1)	Cefazolin, Diazepam, Phytomenadione
2016	5*	26.6±6.5 (20 to 33)	Levetiracetam (2) Barbiturate (2), Gabapentin (2)	Omeprazol
2017	2*	25 and 30	Sodium valproate (1), Topiramate (1), Levetiracetam (1)	Folic acid, Ranitidine
2018	57	28.58±4.13 (19 to 39)	Phenobarbital (54), Levetiracetam (1), Sodium valproate (1), Phenytoin (1)	Folic acid, Cefazolin, Syntocinon
2019	2*	22 and 28	Phenobarbital (1), Sodium valproate (1), Lamotrigine (1)	Triferdin, Folic acid, Calcium Tab, ObiminAZ, Transamin, Senna, Ranitidine

* polytherapy in some patient

AEDs drugs from both old and new group showed high risk of congenital malformation. 9 AEDs drugs have been reported induction minor and major congenital malformation. The result showed our patients use both old and new group of AEDs; 7 AEDs were common drugs induce congenital malformations. AEDs can produce both anatomical and behavioral teratogenicity by the mechanism include; folate deficiency, neuronal suppression, neuronal apoptosis[13]. Risk of CM is dose dependent and polytherapy, but some study show AEDs polytherapy may depend more on the degree of exposure to valproic acid than the number of drugs. Valproic acid was the higher malformation rates, multiple daily administrations did not decrease the risk for malformations, it was likely associated to total daily dose, rather than peak plasma levels[16], and combination of valproic acid with other AEDs were increased CM when compared with monotherapy of other AEDs. The reports from NAAPR pregnancy registries, found the vary prevalence of MCM in difference condition; 9.1% for combination of lamotrigine and valproic acid, 2.9% for lamotrigine plus other AEDs, and 1.9% for lamotrigine monotherapy. In addition, the MCM prevalence of combination of carbamazepine and valproic acid was 15.4%, 2.5% for combination of carbamazepine and any other AED, and 2.9% for carbamazepine monotherapy[17]. Dose-dependency of the MCM risk associated with valproic acid, carbamazepine and lamotrigine have been demonstrated in many study[16].

Although, epilepsy is no longer considered a contraindication to pregnancy, almost of WWE will have good outcomes[14]. The major concern of women with epilepsy were MCM once advised to avoid pregnancy until well controlled of seizure. Well seizure control prior to be pregnant is a good predictor of seizure control during pregnancy. Epilepsy in women with pregnancy is challenging to obstetricians, neurologist, and pediatrics doctors. Pregnancy may alter the sign and symptom of epilepsy are likely to worse. Obstetricians and neurologist also face challenges of inducing risk of congenital while pregnant women intake AEDs, and monitor of late complication by pediatric doctors. There are many support for WWE who used AEDs during pregnancy in any country such as the EURAP (European Registry of Antiepileptic Drugs in Pregnancy), NAAPR (The North American AED Pregnancy Registry), or KREP (The Kerala Registry of Epilepsy and Pregnancy), registry reported and monitoring pregnant women with her child. This study is the first preliminary reported AEDs using in Thai pregnant woman. The pregnancy screening or pregnancy counseling should be recommended in all childbearing WWE, and set-up reporting system for WWE with pregnancy to improve the quality of life in Thai people.

Conclusion

AEDs or epilepsy causes increases the risk of many complications in both maternal and child. It is challenging to obstetricians, neurologist, and pediatric doctors for well co-operation to management of WWE who intake AEDs during pregnant. Finally, pregnant women will have good outcomes postpartum period.

What is already known on this topic?

The antiepileptic drugs using by pregnant women increases the risk of major congenital malformations. There are many study show the differential risks for minor and major congenital malformations from each drugs and dosage. Some country has registration process for recording of the neurodevelopmental effects; impaired cognitive function or late complication, of AEDs at birth to 6 years of age in the children of women who intake AEDs during pregnancy.

What this study adds?

The preliminary report of Thai women with epilepsy (WWE) who intake AEDs during pregnancy, AEDs type, in Srinagarind Hospital, Faculty of Medicine, Khon Kaen University. Planning to prepared registration process to monitoring/following child who give birth by pregnant women with AEDs intake in Thailand.

Acknowledgement

This study was supported in part by the Integrated Epilepsy Research Group, Khon Kaen University, Thailand for paper publication support.

Conflicts of interest

The authors declare no conflict of interest.

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