

T. T. KISPAYEVA, A. S. NURAKHMETOVA  
Karaganda State Medical University

### EPILEPSY AND PREGNANCY: AN ANALYSIS OF THE EFFECTIVENESS OF ANTI-EPILEPTIC DRUGS AND TERATOGENICITY

*Review of the literature devoted to contemporary issues of antiepileptic therapy pregnant various drugs, identifying the most effective of them according to scientific publications from 2006 to 2016. (PUBMED, MEDline, The Cochrane Lb.) It presents the current literature data on the frequency of occurrence of seizures in pregnant women, on the specifics of therapy with antiepileptic drugs (AEDs), the frequency of fetal malformations in pregnant women, taking AEDs regularly, and their dependence on the frequency, dosage and the nature of the therapy. Were studied according to the literature such AEDs as lamotrigine, phenytoin, carbamazepine, valproic acid, phenobarbital, as well as new drugs (vigabatrin, gabapentin, topiramate, tiagabine, oxcarbazepine, levetiracetam, pregabalin). It was found that the risk of birth defects in children observed in the application of high doses of drugs in polytherapy than with monotherapy. The studies revealed new data on the effect of psychotropic drugs on the fetus, allowing them to assess the ratio of "risk / benefit" and to develop recommendations on rational pharmacotherapy in pregnancy in recent years.*

**Keywords:** epilepsy, pregnancy, antiepileptic drugs, teratogenicity.

Achieving a high quality of life for patients suffering from epilepsy, it is the primary task is not only to neurologists, but also for specialists in related disciplines, leading the patient to the subsequent stages of treatment after exhibiting diagnosis [1]. Especially important is the improvement of the quality of life of patients with epilepsy in the gestation period. As the literature suggests, 13% of women epileptic disease escalates during pregnancy [2], which is due to a decrease in the level of antiepileptic drugs (AEDs) in plasma due to the increased metabolism of pregnant [3]. Thus 14% of women seizures observed during pregnancy only [2]. According to foreign studies, aggravation of epilepsy during pregnancy occurs in about 10-13% women with 5% seizure frequency decreases from 85% - does not change [2].

According Lin H. et al. the study of the impact of seizures on fetal weight, gestational age and early preterm birth, direct relationship of seizures and the above pathology has been identified [4]. Developing cramps during pregnancy not only affect the course and outcome of pregnancy, but also in the heart of the fetus during pregnancy and childbirth, on the size, weight, rate of development, the child's cognitive functions. Thus, according to Ozdemir O. et al. the study of the impact of seizures on the fetus in the level of carbon dioxide in arterial umbilical blood was revealed that the fetus suffers a temporary asphyxia during a seizure. At the same time the authors, no association of seizures with cases of chronic hypoxia or prenatal asphyxia [5]. Thus, the presence aggravates epilepsy during pregnancy and childbirth, reduces the weight of the indicators and size of the fetus, gestational age, cognitive function, and therefore the study of the use of pharmacological correction of antiepileptic drugs will improve the above indicators [4,5].

According to the modern classification, AED are divided into the old - barbiturates and hydantoins, basic (most studied) - valproate and carbamazepine, intermediate - succinimides and benzodiazepines, as well as the new era that began in the 1990s, - topiramate, oxcarbazepine, lamotrigine, levetiracetam, pregabalin, felbamate, tiagabine, zonisamide [6].

As shown by recent studies, the application of AEDs is facilitated clinical seizures during pregnancy [7]. At the same time according to Vajda F. et al to assess the consequences in pregnant women who were not taking AEDs, it was found that when using AEDs before pregnancy clinic is facilitated by an epileptic fit during pregnancy. At the same time the use or abandonment of therapy during pregnancy, especially during the first trimester, the degree of malformations does not affect [7].

Other authors mark absence of congenital malformations in children when using AEDs. So, in pregnant women exposed to AEDs, 95.5% of children are born healthy among this population cohort [8].

As the study Bech B. et al. in 16% of cases among women using AEDs, develops spontaneous abortion [9]. At the same time, according to another study on the comparative safety assessment AEDs during pregnancy, through systematic review and meta-analysis found that in the treatment of AEDs may be congenital malformations, as well as the possible loss of the fetus, premature birth [9].

When studying the effects of actions on human placental probe cells on hormones and nutrients were identified lowering RNA cells bearing folic acid, when treated with valproic acid [9]. The authors have shown that further study of AEDs effect on placental barrier is the first step towards a more rational pharmacotherapy and adjunctive treatment of pregnant women with epilepsy [10].

When studying the genotype of the fetus it revealed that placental transport proteins differently directly protect the fetus from the negative effects of many drugs, including the probe, sending back various received in pregnant xenobiotics [2].

As a result of years of research, it was found that the number of congenital malformations was significantly higher at AED polytherapy than with monotherapy [11,12]. At the same time in pregnancy monotherapy revealed 7.08% of cases of congenital malformations in polytherapy - 16.78% of the cases [12]. Rating incidence of congenital malformations in the treatment of epilepsy, according to K. Meador et al. it is recorded as follows: in the treatment of epilepsy, valproic acid, congenital malformations detected in 10.73% cases; phenytoin - 7.36%, phenobarbital - 4.91%, carbamazepine - 4.62%, lamotrigine - 2.91% [12]. Results obtained by studies coordinated with research pharmacology dynamics of AEDs, as a result of which, it was found that phenytoin, levetiracetam, valproate and phenobarbital is likely to pass through the placental barrier to potentially clinically important amounts as gabapentin, topiramate, oxcarbazepine and lamotrigine are the placental barrier to potentially clinically small amount, perhaps, and reduces the risk of congenital malformations [13].

According to Ozdemir O. et al. therapy with phenytoin, carbamazepine, phenobarbital and lamotrigine increases the number of major malformations in two or three times compared with the general population, and the incidence of complications of valproate dose-dependent [11].

At the same time, AED, being a heterogeneous group on structure and mechanism of action, different effects, not only in the placenta [11], the level of cognitive function [14, 15], during pregnancy and childbirth [16], but also have different teratogenic activity [2,8,12]. Thus, Sveberg L. et al. in the course of the study EURAP, which involved 42 countries, 3784 women with epilepsy, we found that the proportion of pregnancies with abortion was significantly higher with valproate (75%), carbamazepine (67.35%), or phenobarbital (73.4%) than in pregnancies in women taking lamotrigine (58.2%) [16]. According Vajda F. et al. levetiracetam has a low teratogenic effects, namely in 0.7% cases, contributes to the development of birth defects and does not affect the intellectual development in children [17]. At the same time, as indicated by Garrity L. et al., levetiracetam is one of the most popular drugs in the treatment of epilepsy in pregnant women should be appointed in certain doses, relieves the attack, with the least negative effect on the fetus [18].

At the same time, according to Eadie M., valproate, too, is not recommended in the treatment, as it has a large list of side effects developing in the fetus [8]. The same opinion is shared by Tomson T., Battino D., alleging that the use of valproate in particular with doses above 800 mg / day increases the risk of teratogenicity [19]. It should be noted that the transition from the next AED is possible, however, such changes must be tested prior to conception [19].

Thus, it should be noted that congenital anomalies are more common with high doses of drugs and the number of simultaneously used [5,12]. An important role is played by genetic factors [3] When you select a drug for a particular patient is recommended to focus on its clinical efficacy. When this showed that lamotrigine and carbamazepine are among the most widely used AEDs, drugs are the safest [12,14,16,17] The incidence of congenital malformations in the background of these drugs is comparable to that of healthy mothers in some cases [8,17]. At the same time, valproic acid has a negative effect on the development of congenital malformations as well as on the performance IQ of children [8,15]. Influence of probe of old and new generation during pregnancy and labor, the development rate in children is practically not been studied and described in the available literature in isolated cases, often a controversial subject that is of great interest to the problem of antiepileptic therapy and in need of further research

#### СПИСОК ЛИТЕРАТУРЫ

- 1 Babenko M. V. To the question of life quality of patients with epilepsy.//Meditsina i ekologiya.- 2012.- 3 (64).- P. 110-112.(In Russ.)
- 2 Atkinson D., Brice-Bennett S. and D'Souza S. Antiepileptic Medication During Pregnancy: Does Fetal Genotype Affect Outcome?// *Pediatr Res.*- 2007.- 62(2).-P. 120-127
- 3 Sabers A. Seizure Control During Pregnancy.// *Harden/Epilepsy in Women.*- 2013. – 1. - P. 91-100
- 4 Lin H., Chen Y., Lin H.. No increase in adverse pregnancy outcomes for women receiving antiepileptic drugs.// *Journal of Neurology.*- 2009.- 256(10).-P. 1742-1749
- 5 Ozdemir O., Sari M., Arpacı Ertugrul F., Kurt A., Selimova V. and Atalay C. The effects of a history of seizures during pregnancy on umbilical arterial blood gas values in pregnant women with epilepsy.//*Journal of the Turkish German Gynecological Association.*- 2014.- 15(3). - P.135-139
- 6 Spina E. Anticonvulsants.// *Encyclopedia of Psychopharmacology.*-2015.-P. 123-127
- 7 Vajda F., O'Brien T., Graham J., Lander C. and Eadie M.. The outcomes of pregnancy in women with untreated epilepsy. // *Seizure.*- 2015.- 24.-P. 77-81
- 8 Nakken, Lillestøl, Brodtkorb E. et al. Antiepileptic drugs and congenital malformations. // *Tidsskr Nor Laegeforen.* - 2014.-134(12-13).- P. 1239-1242.
- 9 Tricco A., Cogo E., Angeliki V., Soobiah C., Hutton B., Hemmelgarn B., Moher D., Finkelstein Y. and Straus S.. Comparative safety of anti-epileptic drugs among infants and children exposed in utero or during breastfeeding: protocol for a systematic review and network meta-analysis.// *Systematic Reviews.*- 2014.- 3(1).- P. 68
- 10 Rubinchik-Stern M., Shmuel M. and Eyal S.. Antiepileptic drugs alter the expression of placental carriers: An in vitro study in a human placental cell line. // *Epilepsia.*- 2015.- 56(7).-P. 1023-1032
- 11 Ozdemir O., Sari M., Kurt A., Sakar V. and Atalay C.. Pregnancy outcome of 149 pregnancies in women with epilepsy: Experience from a tertiary care hospital.// *Interventional Medicine and Applied Science.* -2015.- 7(3).- P.108-113
- 12 Meador K., Reynolds M., Crean S., Fahrbach K. and Probst C.. Pregnancy outcomes in women with epilepsy: A systematic review and meta-analysis of published pregnancy registries and cohorts.// *Epilepsy Research.*- 2008.- 81(1).- P. 1-13
- 13 Harden C., Pennell P., Koppel B., Hovinga C., Gidal B., Meador K., Hopp J., Ting T., Hauser W., Thurman D., Kaplan P., Robinson J., French J., Wiebe S., Wilner A., Vazquez B., Holmes L., Krumholz A., Finnell R., Shafer P. and Le Guen C.. Practice Parameter update: Management issues for women with epilepsy--Focus on pregnancy (an evidence-based review): Vitamin K, folic acid, blood levels, and breastfeeding: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society.// *Neurology.* -2009.- 73(2).- P. 142-149
- 14 Banach R., Boskovic R., Einarson T. and Koren G.. Long-Term Developmental Outcome of Children of Women with Epilepsy, Unexposed or Exposed Prenatally to Antiepileptic Drugs.// *Drug Safety.* – 2010. - 33(1).- P. 73-79
- 15 Meador K., Baker G., Browning N., Clayton-Smith J., Combs-Cantrell D., Cohen M., Kalayjian L., Kanner A., Liporace J., Pennell P., Privitera M. and Loring D. Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs. // *New England Journal of Medicine.* - 2009.- 360(16). - P. 1597-1605
- 16 Sveberg L., Svalheim S. and Taubøll E. The impact of seizures on pregnancy and delivery. // *Seizure.*- 2015.- 28.- P. 35-38
- 17 Vajda F., O'Brien T., Graham J. and Eadie M.. The efficacy of the newer antiepileptic drugs in controlling seizures in pregnancy.// *Epilepsia.*- 2014.- 55(8).- P.1229-1234
- 18 Garrity L., Turner M. and Standridge S.. Increased Levetiracetam Clearance Associated with a Breakthrough Seizure in a Pregnant Patient Receiving Once/Day Extended-Release Levetiracetam. *Pharmacotherapy.*// *The Journal of Human Pharmacology and Drug Therapy.*- 2014.- 34(7). – P.128-132
- 19 Tomson T. and Battino D.. Pregnancy and epilepsy: what should we tell our patients? // *Journal of Neurology.*- 2009. - 256(6). –P. 856-862

## ЭПИЛЕПСИЯ И БЕРЕМЕННОСТЬ: АНАЛИЗ ЭФФЕКТИВНОСТИ И ТЕРАТОГЕННОСТИ ПРОТИВОЭПИЛЕПТИЧЕСКИХ ПРЕПАРАТОВ

**Резюме:** Обзор литературы посвящен современным вопросам противоэpileптической терапии беременных различными препаратами с выявлением наиболее эффективного из них по данным научных публикаций с 2006 по 2016 года. (PUBMED, MEDline, The Cochrane Lb.) Представлены современные литературные данные по частоте встречаемости судорожного синдрома у беременных, по особенностям терапии противоэpileптическими препаратами (ПЭП), по частоте внутриутробных пороков развития среди беременных, принимавшие регулярно ПЭП и их зависимость от частоты, дозировки и характера проводимой терапии. Были изучены по литературным данным такие ПЭП, как ламотриджин, фенитоин, карбамазепин, вальпроевая кислота, фенобарбитал, а также новые препараты (вигабатрин, габапентин, топирамат, тиагабин, окскарбазепин, леветирацетам, прегабалин). При этом было установлено, что риск развития врожденных пороков у детей наблюдаются при применении высоких доз препаратов при политерапии, чем при монотерапии. В исследованиях последних лет выявлены новые данные о влиянии психотропных препаратов на плод, позволяющие оценивать их соотношение «польза/риск» и разрабатывать рекомендации по рациональной фармакотерапии у беременных.

**Ключевые слова:** эпилепсия, беременность, противоэpileптические препараты, тератогенность.

**Т.Т. КИСПАЕВА, А.С. НУРАХМЕТОВА**

*Қарағанды мемлекеттік медицина университеті*

## ЭПИЛЕПСИЯ ЖӘНЕ ЖҮКТІЛІК: ЭПИЛЕПСИЯҒА ҚАРСЫ ПРЕПАРАТТАРДЫҢ ТИІМДІЛІГІ ЖӘНЕ ТЕРАТОГЕНДІГІНІҢ ТАЛДАУЫ

**Түйін:** Бұл әдебиеттерге шолу 2006-2016 жылдардағы ғылыми публикациялар бойынша ең тиімді нәтиже көрсеткен препараттарды анықтай отырып, жүкті әйелдердің эпилепсияға қарсы терапиясының қазіргі замандағы мәселелеріне арналады. Және де жүкті әйелдерде кездесетін ұстама синдромының жиілігі бойынша, эпилепсияға қарсы препараттардың терапия ерекшеліктері бойынша, жүкті әйелдер арасында ұрықтың даму кемістігі, жиілігі бойынша, эпилепсияға қарсы препараттарды тұрақты қабылдаған жүкті әйелдердің сол препараттарға тәуелділігі, препараттарды қабылдаудың жиілік сипаты бойынша жаңа деректер берілген. Бұл әдебиет деректері бойынша эпилепсияға қарсы препараттар: ламотриджин, фенитоин, карбамазепин, вальпрой қышқылы, фенобарбитал және жаңа препараттар: вигабатрин, габапентин, топирамат, тиагабин, окскарбазепин, леветирацетам, прегабалин сияқты препараттар бойынша деректер зерделенді. Осы деректер бойынша монотерапияға қарағанда политерапияда препараттардың мөлшерден көп дозасын қабылдау кезінде балаларда туа біткен кемістіктердің көбеюі анықталды. Соңғы жылдардағы зерттеулер нәтижесі психотропты препараттардың ұрыққа әсер ету жөнінде жаңа деректерін анықтады. Ол препараттардың пайдасы немесе зияны ара- қатынасын бағалау мүмкіндіктерін беруге және жүкті әйелдерге тиімді фармакотерапия бойынша жаңа ұсыныстар әзірленді.

**Түйінді сөздер:** эпилепсия, жүктілік, эпилепсияға қарсы препараттар, тератогендік