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 is 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 hydantoin, 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. the study of the impact of seizures on 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 research of years, 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 (67.3%), 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 Edie 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.

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Т. Т. КИСЛАЕВА, А. С. НУРХАМЕТОВА
ЭПИЛЕПСИЯ И БЕРЕМЕННОСТЬ: АНАЛИЗ ЭФФЕКТИВНОСТИ И ТЕРАТОГЕННОСТИ ПРОТИВОЭПИЛЕПТИЧЕСКИХ ПРЕПАРАТОВ

Резюме: Обзор литературы посвящен современным вопросам противоэпилептической терапии беременных различными препаратами с выявлением наиболее эффективного из них по данным публикаций с 2006 по 2016 года. (PUBMED, MEDline, The Cochrane Lib.) Представлены современные литературные данные по частоте встречаемости судорожного синдрома у беременных, по особенностям терапии противоэпилептическими препаратами (ПЭП), по частоте внутриутробных пороков развития среди беременных, принимавших 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, также новые препараты (вигабатрин, габапентин, тиагабин, окскарбазепин, прегабалин). При этом было установлено, что риск развития врожденных пороков у детей наблюдается при применении высоких доз препаратов при полигемиапии, чем при монотерапии. В исследованиях последних лет выявлены новые данные о влиянии психотропных препаратов на плод, позволяющие оценивать их соотношение «польза/риск» и разрабатывать рекомендацию по рациональной фармакотерапии у беременных.

Ключевые слова: эпилепсия, беременность, противоэпилептические препараты, тератогенность.

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