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Peculiarities of Epilepsy Treatment in Women of Childbearing Age

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Annotation. The article is devoted to the peculiarities of epilepsy treatment in women of childbearing age. Physiological peculiarities of this category of patients, neuroendo-crine disorders, which may be a consequence of both the disease itself and the therapy administered, are discussed in detail. The data presented in the article indicate the need for a differentiated approach to the management of these patients, as well as the correct choice of antiepileptic drugs (AEDs) depending on the form of epilepsy, the type of seizures, and the potential effect of AEDs on hormonal status. When choosing antiepileptic drugs in girls and women of fertile age, preference should be given to new-generation drugs (lamotrigine and levetiracetam), taking into account the medicinal aspects of these drugs (interaction of AEDs among themselves, with hormonal contraceptives, the effect of drugs on the menstrual cycle, fertility indicators, teratogenicity).

Keywords: epilepsy; epilepsy in women; pregnancy; antiepileptic therapy; teratogenicity

Introduction

The problem of epilepsy treatment in women of childbearing age is becoming increasingly important nowadays. According to the results of various studies, active epilepsy patients make up on average about 1% of the population; in economically developed countries this figure is somewhat lower (0.6-0.8%), and in countries with a low economic level it may reach 1.2-1.5% and higher. Between 25 and 40% of all epileptic patients are women of childbearing age. According to LAC (2007), about 500,000 women of childbearing age in the USA have epilepsy. Up to 0.7% of pregnant women have epilepsy, 13% of them manifest during pregnancy and 14% develop gestational epilepsy. About 3-5 babies per 1000 are born to mothers with epilepsy, which requires a very cautious approach to prescribing antiepileptic drugs (AEDs) not only during pregnancy but also to all women of childbearing age. The treatment of epilepsy in women is a complex problem. It is not by chance that in recent decades the gender aspect of epilepsy therapy has received increased attention. This is due, on the one hand, to a number of physiological features of the female organism, psychological and social peculiarities, and, on the other hand, to significant side effects of antiepileptic therapy on the female organism. The treatment of epilepsy in women during periods of physiological hormonal changes: puberty, pregnancy, childbirth and lactation, menopause, is particularly difficult. In addition, the female organism is inherent in the monthly cyclical changes in the hormonal background. A number of specific forms of epilepsy and epileptic syndromes are associated with these hormonal changes: polo-dependent Aicardi and Rett syndromes, catamenial epilepsy, photosensitive epilepsy. Epileptic seizures, in turn, have an adverse effect on hormonal status, disrupt puberty, fertility, and have a significant teratogenic effect. Women with epilepsy have lower fertility rates, frequent anovulatory menstrual cycles. Women with epilepsy are known to be 25-30% less likely to become pregnant and bear a child than women in the general population. Reduced fertility in women with epilepsy can be explained

by several reasons. First of all, these are structural and functional peculiarities of the hypothalamic-pituitary-gonadal system and the relationship with the limbic system. Persistence of epileptic activity leads to dysfunction of these structures, changes in hormonal status and a decrease in estrogen levels. Epileptic seizures cause an increase in prolactin levels, which suppresses ovulation by affecting the hypothalamic-pituitary-adrenal system. Administration of many basic AEDs (phenytoin, carbamazepine, phenobarbital, primidone, tiagabine) increases the synthesis of hormone-binding proteins and induces an increase in the activity of hepatic enzymes. This leads to a decrease in the concentration of endogenous free sex hormones in blood plasma. Despite the slight prevalence of male patients with epilepsy in the population of epileptic patients, the prevalence of epilepsy in women is significantly higher during puberty (manifestation at 10-14 years of age is significantly predominant in girls, the second peak of incidence after early childhood) and up to 30 years of age, as well as after 70 years of age. The pubertal period is characterised by the beginning of cyclic functioning of the hypothalamic-pituitary-gonadal system with an alternative influence of steroid (estradiol and progesterone) sex hormones on epileptic activity and a significant increase in metabolic processes. In the pubertal period, the so-called catamenial (menstrual) epilepsy debuts, in which epileptic seizures are closely associated with a particular phase of the menstrual cycle. There is a significant predominance of generalised convulsive epilepsies in the structure of catamenial epilepsy. Even Hippocrates pointed out that delayed mensis may contribute to the development of seizures. Usually epileptic seizures are more frequent during the perimenstrual period, but they also occur at other times and are much less frequently (about 12%) associated only with a particular phase of the cycle. The highest frequency of seizures is observed with increasing levels of estradiol and decreasing progesterone in the blood (luteal phase and the first days of menstruation). Neuroendocrine disorders are detected in 58% of patients with catamenial epilepsy (hyperprolactinaemic syndrome, polycystic ovaries, hypothyroidism).

Epilepsy is one of the few serious neurological conditions that requires continuous long-term treatment during pregnancy. Epileptic seizures have a significant impact on maternal health and can lead to maternal death (Cantwell et al., 2011). Moreover, frequent generalised tonic-clonic seizures are often an independent risk factor for postnatal cognitive decline in children.

Seizure frequency is known to remain unchanged during pregnancy in 47-83% of cases (mean ~70%) (Guveli B.T. et al., 2017), and according to the European and International Registry of Antiepileptic Drugs in Pregnancy (EURAP), in 64% of cases, and in 93% of them complete seizure control is registered. As a result of the complex interaction of a number of physiological factors during pregnancy, seizure frequency may increase or decrease due to changes in circulating steroid levels, increased circulating blood volume and cardiac output, increased renal filtration, postural hypotension, anaemia, increased metabolic rate, and insulin resistance. The pharma-cokinetic profile of AEDs also plays a major role in altering seizure frequency in pregnancy.

Changes in seizure frequency during pregnancy:

- 3-24 % - reduction of seizures;
- 14-32 % - increased frequency of seizures;
- 47-83% - no significant change;
- achieving medication remission 9-12 months before pregnancy is a predictor of seizure-free pregnancy (84-92%) (level of evidence B).

Despite the significant risk of complications with AEDs, there is no doubt that epilepsy requires continued treatment during pregnancy. Seizures during pregnancy should be treated not only to improve the quality of life of the mother, but also to prevent seizure-related injuries, status epilepticus and other serious life-threatening complications. Seizures during pregnancy pose the most significant threat to the foetus (Saho and Klein, 2005). For example, seizures during pregnancy and labour disrupt the fetal heart rate, lead to hypoxia and prolonged uterine spasm, haemorrhage, uterine rupture and fetal death. Placental abruption has been described in more than 5% of mild injuries and 50% of serious injuries due to seizures during

pregnancy. Epileptic seizures develop during labour and within the next 24 hours in 5% of women, posing a significant threat to the baby and mother. Status epilepticus develops in 1-3% of women during pregnancy.

On the other hand, despite the large number of studies, there is no reliable data on the increased risk of major complications in pregnant women with epilepsy such as preterm labour, gestational diabetes, intrauterine fetal death, perinatal fetal death or the need for resuscitative measures for the baby, compared to general population data (Vile et al., 2015).

Complications of pregnancy (increased risk):

- pre-eclampsia (level of evidence U);
- caesarean section - 1.5-fold increase (level of evidence C);
- arterial hypertension (level of evidence U);
- preterm labour - no significant increase in risk, but smoking women have a significantly increased risk of preterm labour (level of evidence: C);
- haemorrhage - 1.5-fold increase (level of evidence B);
- spontaneous abortion (level U);
- status epilepticus (level of evidence U).

Taking AEDs during pregnancy, regardless of whether the drug is prescribed for epilepsy or other conditions (chronic pain syndromes, psychiatric disorders, migraine), is associated with a significant risk of large congenital malformations, averaging 4-8% (10% or more with polytherapy), as these drugs pass through the fetoplacental barrier. In the general population, the risk of malformations is 2-3 %.

Malformations - persistent morphological changes of an organ, system or organism beyond their structure, as a result of disruption of embryonic development. Minor anomalies - insignificantly varying structural deviations from the norm that do not require medical or surgical correction. The frequency of malformations in children born to mothers with epilepsy (taking and not taking AEDs) exceeds the population data by 1.2-2 times. The first data on teratogenic effects of AEDs were published in the 1960s (Janz D., Fuchs U., 1964; Meadow S.R., 1968), and since then, studies on the side effects of AEDs during pregnancy have continued. A number of syndromes (combinations of various malformations) characteristic of taking certain AEDs, the so-called Fetal Anticonvulsant Syndromes, have been identified:

- Fetal Hydantoin Syndrome (FHS);
- PrimidoneEmbryopathy;
- Fetal Trimethadione Syndrome;
- Fetal Phenobarbital Syndrome;
- Fetal Valproic Acid Syndrome;
- Fetal Carbamazepine Syndrome.

The most frequent teratogenic effects of AEDs are incongruence of the upper lip and palate, congenital heart disease, urogenital defects, and defects in the development of the fetal nervous system. In children born to mothers who have taken AEDs, such malformations are registered 2-3 times more often than in the population. Malformations and delayed cognitive development are among the most frequent delayed complications of AED administration. According to the UK Epilepsy and Pregnancy Register (UK Epilepsy and Pregnancy Register, 2009), there is an increase in the number of both small and large malformations, which is highly dependent on whether the woman was taking mono- or polytherapy, which AED she was taking, and which AED she was taking

Large congenital malformations

Phenytoin

Fetal hydantoin syndrome, congenital heart pathology, orofacial clefts

Valproate

Neural tube defects, craniofacial, skeletal, cardiovascular, cerebral defects

Carbamazepine

Neural tube defects, congenital cardiac pathology, short stature, hypospadias

Barbiturates

Craniofacial defects, congenital heart pathology, limb pathology, short stature

Benzodiazepines

Orofacial clefts

Lamotrigine

Single reports of orofacial clefts

Table 1. Most frequent teratogenic effects of AEDs (Vajda et al., 2014; Vionescu and Penelli, 2015)

(or combination of AEDs) and from the dosage of the drugs.

According to the registry data, small malformations were observed in 6-20% of newborns (resequinovarus, hypo-aspadias, dysplasia of the finger phalanges, hypertelorism, epicanthus).

Thus, the risk of fetal complications when a mother takes AEDs is quite significant, but seizures of any type in the first trimester of pregnancy have been found to increase the risk of malformations in children to 12.3% compared to 4% (8%) in children from mothers with epilepsy but without seizures during pregnancy. To date, no major guidelines have developed clear and unambiguous contraindications to pregnancy in women with epilepsy.

Recommendations

The UK and LAC standards do not specify contraindications to pregnancy and childbirth (only general recommendations). Pregnancy is recommended in cases of persistent medication remission and in subcompensation with infrequent seizures.

Based on a number of European and American recommendations, the basic principles of epilepsy treatment in pregnant women can be formulated as follows:

1. Pregnancy in women with epilepsy should be planned whenever possible, including to adjust the doses of AEDs and in some cases to switch to monotherapy.

2. The safest drug is the one that maximises seizure control.

3. no change in treatment is indicated in early pregnancy, especially effective treatment.

4. During pregnancy, the lowest dose of AED that effectively controls seizures should be prescribed whenever possible.

5. Cancellation of AEDs is considered on a case-by-case basis, preferably switching to monotherapy. AEDs should not be replaced if the patient is in remission, as this is a predictor of seizure absence in most cases during pregnancy.

6. Long-acting drugs should be favoured.

Management of pregnant women with epilepsy.

In compensated condition with remission of seizures, regular follow-up by a neurologist once every 2 months, by an obstetrician-gynaecologist - according to the norms.

In case of persistence of seizures, the regularity of observation by a neurologist - once a month; by an obstetrician-gynaecologist - once every 2 weeks.

Patients should be aware of the need to consult a neurologist when seizures become more frequent.

If seizures become more frequent, the dose of AEDs should be increased or a new drug should be added.

EEG should be performed in compensated course once every 2 months, in case of persistence of seizures - at every visit to a neurologist.

It is desirable to determine the concentration of AEP before the beginning of pregnancy, and then at the beginning of each trimester and in the last 4 weeks before delivery.

The concentration of hormones of the fetoplacental complex (placental lactogen, progesterone, estriol, cortisol) and alpha-fetoprotein is examined from the end of the 1st trimester onwards at least once a month.

Dynamic ultrasound of the foetus - at registration, at 11-12 weeks, at 19-21 weeks and subsequently once every 4 weeks.

From the 20th week onwards, given the high risk of fetoplacental insufficiency, it is justified to perform Doppler ultrasound examination of blood flow in the umbilical artery, aorta and middle cerebral artery of the foetus (if indicated).

When performing ultrasound fetometry, the possible effects of AEDs should be taken into account. Taking into account the risk of congenital pathology (all AEDs are potentially teratogenic), it is mandatory to consult a geneticist before the 17th week of pregnancy, if indicated - chorion biopsy, amniocentesis with determination of alpha-fetoprotein concentration in amniotic fluid and cytogenetic study.

There is a risk of haemorrhagic complications in children from mothers who took carbamazepine, diphenine, primidone, phenobarbital. This is due to vitamin K deficiency. Women taking these drugs should prophylactically take Vika-sol 1 time a day from the 36th week of gestation until delivery, and children are injected with vitamin K intravenously immediately after delivery.

Diagnosis and treatment of fetoplacental insufficiency are carried out according to standard schemes.

Epilepsy is not a contraindication for delivery through natural labour.

Indications for operative delivery are tendency to serial course, epileptic status, significant increase in the frequency of seizures, pre-eclampsia with a severe course, negative dynamics of fetal condition. Drug therapy is a priority for epilepsy in women, but it is not sufficient to consider only the appropriateness of the prescribed drug for the form of epilepsy and the type of epileptic seizures. The drug aspect involves taking into account the interaction of AEDs (or several jointly prescribed antiepileptic drugs) among themselves, with hormonal contraceptives, the effect of drugs on the menstrual cycle, fertility indicators, teratogenicity.

Unfortunately, the prescription of such effective and most widely used antiepileptic drugs (AEDs) as valproates, phenytoin, carbamazepines may be undesirable in girls and women of fertile age: Valproates during puberty cause polycystic ovaries, menstrual disorders, mastitis, weight gain; prolonged use of phenytoin leads to a number of cosmetic defects, carbamazepines, by inducing the enzyme system, reduce the effectiveness of hormonal contraceptives and hormone replacement therapy. In addition, taking enzyme-inducing AEDs leads to impaired bone mineral metabolism and, as a consequence, to the development of osteoporosis.

Older generation AEDs (phenobarbital, phenytoin) and valproates have a significantly higher risk of teratogenicity than lamotrigine, levetiracetam, clonazepam and gabapentin (Banguar S. et al., 2016). The International Antiepileptic League has made key recommendations (Tack Forse of ILAE-Commission on European Affairs and EAN 2015-2016) restricting the use of valproic acid in women: valproate '...should not be used in female children and adolescents, in women of childbearing age and in pregnant women, unless unless other drugs are ineffective or intolerable...' If valproic acid preparations are to be used, dosages exceeding 500-600 mg/day are not recommended. (North American Antiepileptic and Pregnancy Register, 2012 and UK Irel and Pregnancy Register, 2014), while the EURAP register (2011) shows a significant reduction in teratogenicity at doses not exceeding 700 mg/day.

Analysis of a number of registries suggests that in recent years there is sufficient evidence that newer generation AEDs (lamotrigine and levetiracetam) have advantages when used in girls and women of childbearing age as first-line monotherapy, as they do not confer a significant risk of increased teratogenicity compared to controls (Veroniki et al., 2017). Moreover, even polytherapy with lamotrigine and levetiracetam does not increase the risk of malformations compared to monotherapy with these drugs. There is sufficient evidence for the use of lamotrigine in women of childbearing age and pregnant women. The lowest risk of malformations is observed with lamotrigine doses < 300 mg/day (according to the UK Registry, > 200 mg/day), while the risk of terato-genicity almost doubles with doses greater than 300 mg/day (Tomson T. et al., 2010).

Lamotrigine may be the drug of choice for first-line monotherapy in women of fertile age. It is as effective as valproate and car-bamazepine in the treatment of partial, secondary-generalised and primary-generalised seizures (excluding absences and myoclonic seizures), with minimal side effects on female genitalia and metabolism. However, there is a fairly significant decrease in lamotrigine levels (in the 2-3rd trimester), which may be accompanied by increased frequency or recurrence of seizures. Administration of lamotrigine in pregnant women requires monitoring of plasma concentration of the drug and dosage adjustment in 20-30% of cases.

A number of clinical and experimental studies have been conducted on the effect of levetiracetam on reproductive function. No disturbances of fertility and reproductive function in experimental animals at doses of 1800 mg/kg/day (6-fold exceeding the maximum dose for humans) were observed. The UK Epilepsy and Pregnancy Register (UK Epilepsy and Pregnancy Register; 362 observations over 15 years, 1996-2009) analysed pregnancy outcomes in patients taking levetiracetam over a 15-year period. Only 9 large malformations were reported in the babies of 229 patients taking polytherapy with levetiracetam, which was less than 4%. Whereas, according to EURAP (2009), the average rate of malformations when taking other AEDs in polytherapy is 9.2 %. No malformations were recorded in 133 observations in monotherapy. No differences in the cognitive development of children compared to population data were also found. It is possible to cite data from some of the largest studies in recent years in Europe and the United States, which indicate the maximum possible safety of the use of levetiracetam during pregnancy at the present time

Levetiracetam is characterised by a significant decrease in plasma levels (by 40-60%) in the 3rd trimester of pregnancy, which may be accompanied by increased frequency or recurrence of seizures. This requires monitoring of plasma concentration and correction of the daily dosage of the drug. Levetiracetam levels recover rapidly within 2 weeks after delivery, which also requires consideration and dosage modification. Despite the significant content of levetiracetam in breast milk, low concentrations of the drug (< 10-15 mM) are registered in the plasma of newborns.

Our series of clinical studies (2008-2012) also confirmed that lamotrigine and levetiracetam practically do not change the hormonal background in adolescent girls and women, do not provoke the development of osteoporosis, do not cause weight changes and cosmetic defects.

Studies of the use of vagus stimulators (VNS) in pregnant women are of sufficient interest. However, the sample size is insufficient to draw any firm conclusions about the safety of VNS in pregnancy. Preliminary data suggest an increased frequency of obstetric interventions in such patients and no clear association with increased thera-togenicity. Our series of clinical studies (2008-2012) also confirmed that lamotrigine and levetiracetam practically do not change the hormonal background in adolescent girls and women, do not provoke the development of osteoporosis, do not cause weight changes and cosmetic defects.

Studies of the use of vagus stimulators (VNS) in pregnant women are of sufficient interest. However, the sample size is insufficient to draw any firm conclusions about the safety of VNS in pregnancy. Preliminary data suggest an increased frequency of obstetric interventions in such patients and no clear association with increased thera-togenicity. The next question usually concerns breastfeeding of children when the mother is taking AEDs. Absolutely all recommendations and studies are unanimous in the opinion that refusal of breastfeeding is unjustified, because during pregnancy and labour the level of AEDs in blood is usually higher than in mother's milk. ‘

From a practical point of view, when the mother takes high doses of some AEDs that can cause sedation of the baby (phenobarbital, phenytoin, carbamazepine), it can be recommended to replace several feedings (2-3) with artificial nutrition.

Folic acid administration 2-3 months before pregnancy and during the 1st and 2nd trimester of pregnancy from 0.4 to 4-5 mg/day is generally recommended as adjunctive therapy to reduce the risk of malformations (especially neural tube abnormalities) (level of evidence C). Maternal administration of

enzyme-inducing AEDs requires administration of vitamin K p/k 1 mg/kg immediately after birth (level U). B vitamins are also commonly administered during pregnancy as part of a total complex.

Conclusions

1. The presence of maternal epilepsy cannot be a contraindication to childbearing, except in non-curable cases, significant psychiatric disorders and the presence of obstetric contraindications.

2 Pregnancy in women with epilepsy should be planned and monitored according to the rules outlined in the 'Ushfshovanu kshchkochnogo protocol^...' (Ministry of Health of Ukraine, 2014).

3 Medication treatment of epilepsy continues during pregnancy, it is desirable to change AED therapy before the onset of pregnancy at the planning stage (9-12 months in advance). Switching to monotherapy is desirable.

4. When choosing AEDs in girls and women of fertile age, preference should be given to new generation drugs (lamotrigine, levetiracetam) taking into account their minimal impact on the hormonal profile and the lowest teratogenicity.

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