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Integrative Acuery-Neurological Management of Pregnant with Epileptic Disorders

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Abstract Epilepsy is one of the most common chronic neurological diseases affecting approximately 65 million people worldwide. Among women of reproductive age, the prevalence of epilepsy is 0.3-0.8%, which corresponds to approximately 1.1 million women of childbearing age in Europe alone. Every year, more than 1.2 million pregnancies are registered in women with epilepsy worldwide, which is 0.3-0.5% of the total number of births. Pregnancy in women with epilepsy is a unique medical situation characterized by a complex interaction between epileptic seizures, anti-epileptic therapy, physiological changes in pregnancy, and fetal development. This problem requires an integrated approach involving a multidisciplinary team of specialists, including obstetrician-gynecologists, neurologist-epileptologists, clinical pharmacologists, geneticists, neonatologists, and child development specialists.

Keywords Epilepsy, Pregnancy, Anti-epileptic drugs, Teratogenicity, Multidisciplinary management, Maternal outcomes, Perinatal outcomes, Preconception counseling, Folic acid, Neurodevelopment, Therapeutic monitoring, Obstetric complications, Prenatal diagnostics

1. Introduction

The influence of pregnancy on the course of epilepsy is individual and can vary significantly. In 15-32% of pregnant women, there is an increase in epileptic seizures, especially in the first and third trimester of pregnancy [1]. This is due to many factors: changes in the pharmacokinetics of anti-epileptic drugs (EPPs) due to increased distribution volume, increased renal clearance, decreased protein binding, and induction of liver enzymes; hormonal fluctuations (progesterone has anticonvulsant activity, estrogens can provoke seizures); psychosocial factors (stress, anxiety, sleep deprivation); decreased adherence to therapy due to fear of teratogenic effects [2].

Antiepileptic therapy during pregnancy presents a complex clinical dilemma that requires balance between adequate control of the mother's seizures and minimizing the risk to the developing fetus. Practically all PEPs penetrate the placental barrier and possess a certain teratogenic potential. The risk of major developmental defects (MDR) when exposed to PPE is 4-9% compared to 2-3% in the general population. The highest teratogenic risk is associated with valproic acid (6-20% depending on the dose), phenytoin (7-10%), carbamazepine (4-6%), and phenobarbital (5-7%). Lamotrigine (2-3%), levetiracetam (2-2.5%), and oxcarbazepine (2-3%) are considered relatively safe [3].

The dose-dependent nature of the teratogenic effect of most PPs emphasizes the importance of using minimal effective doses. Polytherapy is associated with a higher risk of BPR (up to 15-20%) compared to monotherapy, which makes it preferable to use one drug at the maximum tolerated dose. Folat deficiency conditions in pregnant women with epilepsy pose a particular problem. Many PEPs (valproic acid, carbamazepine, phenytoin, phenobarbital, primidone) are antagonists of folic acid, disrupting its absorption, metabolism, and utilization. Folate deficiency increases the risk of neural tube defects by 3-5 times, which justifies the prescription of high doses of folic acid (4-5 mg per day) to all women with epilepsy of reproductive age [4]. Cognitive and behavioral impairments in children exposed to intrauterine PE are a long-term problem, often surpassing structural malformations. Intrauterine exposure to PEP can lead to a decrease in the intelligence quotient, speech developmental disorders, specific learning difficulties, autism spectrum disorders, and attention deficit hyperactivity syndrome [5]. Valproic acid has the most pronounced negative effect on neurodevelopment, especially in doses exceeding 1000 mg per day.

Obstetric complications in women with epilepsy are significantly more common than in the general population. The frequency of cesarean section reaches 25-40%, which is 1.5-2 times higher than the population indicators. The increased frequency of surgical delivery is due to both medical indications (frequent attacks, development of

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epileptic status, fetal developmental anomalies) and psychosocial factors (increased anxiety of patients and medical personnel). The risk of developing epileptic seizures during childbirth is 1-4%, while generalized tonic-clonic seizures can lead to fetal hypoxia, premature placental abruption, traumatic injuries, and other serious complications [6]. Premature births in women with epilepsy are 1.5-2 times more common (8-15% vs. 5-7% in the general population), which can be related to both the direct influence of epileptic seizures and the side effects of PEP. Intrauterine fetal developmental delay is observed in 10-20% of pregnant women with epilepsy, which requires careful monitoring of fetal growth and timely correction of obstetric tactics [7].

The postpartum period in women with epilepsy is characterized by an increased risk of seizures due to sharp changes in the pharmacokinetics of PPE, hormonal fluctuations, sleep deprivation, and stress. In 15-25% of women, there is a deterioration in the control of seizures in the first 48-72 hours after childbirth, which requires correction of antiepileptic therapy.

Breastfeeding for epilepsy is possible in most cases, since the concentration of PEP in breast milk is usually 10-60% of the mother's plasma concentration. This excludes ethosuximide, levetiracetam, and lamotrigine, which penetrate breast milk in higher concentrations. Nevertheless, the benefits of breastfeeding usually outweigh the potential risks. The psychosocial aspects of pregnancy in epilepsy include increased frequency of depressive disorders (up to 40%), anxiety states (up to 60%), social stigmatization, and discrimination. Up to 35-40% of women with epilepsy avoid pregnancy due to fear of hereditary transmission of the disease, despite the fact that the genetic risk in most cases does not exceed 3-9% [8].

Preconception counseling is a cornerstone of successful pregnancy management in women with epilepsy. It should be carried out 3-6 months before planned conception and include optimization of anti-epileptic therapy with transition to drugs with the lowest teratogenic potential, prescription of high doses of folic acid, lifestyle correction, information about risks and methods of their minimization. Unfortunately, only 25-35% of women with epilepsy receive adequate preconception counseling. Modern principles of pharmacotherapy for epilepsy during pregnancy are based on the use of monotherapy in minimal effective doses using drugs with the lowest teratogenic risk. If polytherapy is necessary, rational combinations of drugs with different mechanisms of action and synergistic effect are preferred. Therapeutic drug monitoring of PEP concentrations plays a key role in maintaining optimal control of seizures against the backdrop of changing pharmacokinetics [9].

Prenatal diagnosis in pregnant women with epilepsy requires a specialized approach with extended ultrasound screening, including a detailed assessment of the structures of the brain, heart, limbs, and other organs at 16-18 and 20-24 weeks of pregnancy. Determining the level of α-fetoprotein in the mother's serum at 15-20 weeks of pregnancy allows for the detection of nerve tube defects, the risk of which increases when using PEP [10].

Neonatal problems in children from mothers with epilepsy include neonatal hemorrhagic syndrome (especially when using liver enzyme inducers), PEP cancellation syndrome, respiratory disorders, and adaptation difficulties. Preventive administration of vitamin K is recommended for all newborns from mothers receiving phenytoin, carbamazepine, phenobarbital, or primidone. Monitoring of the development of children exposed to intrauterine PEIs should continue during the first years of life with regular assessment of psychomotor, speech, and cognitive development. Early detection of developmental disorders allows for timely initiation of corrective measures and improvement of long-term outcomes [11].

Organizational aspects of medical care for pregnant women with epilepsy include the creation of specialized centers, the development of standardized management protocols, the training of medical personnel, and the creation of pregnancy registers for epilepsy for long-term monitoring of the safety of PEP. Modern technological solutions, including telemedicine consultations, wearable devices for monitoring seizures, and mobile applications for keeping diaries of symptoms, open up new opportunities for optimizing the management of pregnant women with epilepsy, especially in conditions of limited availability of specialized medical care [12]. The purpose of the study: to analyze the current state of the problem of obstetric and neurological support for pregnant women with epilepsy and to develop scientifically sound approaches to optimizing medical care for this category of patients.

2. Research Material and Methods

We examined the clinical characteristics of the women examined, the results of retrospective and prospective studies. Pregnant women were selected to participate in the study. All the subjects were divided into two groups: healthy women and an experimental group – pregnant women with epilepsy. Taking into account the initial tasks and goals, we have developed a research program that includes clinical and statistical analysis, neurophysiological, hormonal, functional and pathomorphological studies. The subsequent mathematical processing of the data was carried out by methods of variational statistics using standard computing program In addition, the study identified a control group consisting of 53 women with conditional good health who were under medical supervision at the consultative polyclinic No. 17 in Tashkent.

3. The Results of the Study

The age of women from the main and control groups ranged from 18 to 40 years. To analyze the fetal condition, a biophysical profile (BFPP) was used (a comprehensive assessment of 6 parameters according to the A. Vintzileos method): 1. Fetal respiratory activity. 2. Fetal motor activity.

3. Fetal muscle tone. 4. Assessment of the amount of amniotic fluid. 5. Stress-free cardiotocography test: included an assessment of the response of fetal cardiac activity to various stimuli, while studying the response of fetal heart rate to the movements and activity of the mother. 6. The degree of maturity of the placenta according to Grannum: the degree of maturity of the placenta was assessed using an assessment system developed by Grannum. An analysis of the somatic anamnesis of both groups of patients showed the presence of an average of one or two pathologies.

In the first group, generalized idiopathic epilepsy was diagnosed in 55 (50.9%) women, and 53 (49.1%) had partial locally caused epilepsy. Of these, 37 (69.8%) had symptomatic epilepsy, and 16 (30.1%) had cryptogenic epilepsy. In the second group, generalized idiopathic epilepsy was diagnosed in 42 (51.2%) women, partial locally caused epilepsy in 40 (48.7%). Among them, 31 (73.8%) had symptomatic epilepsy, and 11 (26.2%) had cryptogenic epilepsy. Thus, the two groups were comparable in terms of types of epilepsy. As for monotherapy, in the first group there were 29 (76.3%) pregnant women who received monotherapy with antiepileptic drugs. Of these, 43 (40.9%) women took valproic acid medications, and 62 (59.1%) took carbamazepine.

In the group where treatment with two or more anticonvulsants was used, the benefit of treatment was also predominant. In 31 (73.8%) gestational women with generalized idiopathic epilepsy and in 24 (77.4%) pregnant women with locally caused cryptogenic epilepsy, treatment with two or more anticonvulsant drugs showed a successful result.

It can be seen that the most frequent fetal deterioration in epilepsy in women during gestation in the second group were chronic fetoplacental insufficiency (42.6%) and acute fetal hypoxia during childbirth (10.9%). Compared with the first group, where these indicators were 11.1% and 5.3%, respectively, these differences are statistically significant ($p<0.05$). There were no cases of intrauterine fetal death in any of the groups under consideration. It is extremely important to emphasize that one of the closest complications observed in newborns from mothers diagnosed with epilepsy in group 2 was fetal adynamia, noted in 34.1% of cases, compared with 12.9% in group 1 ($p<0.01$). An analysis of the frequency of pathological disorders in fetuses and newborns, depending on the treatment, revealed that developmental pathologies were noted only in the 2nd group, and its indicators were 3.6%. At the same time, the nature of congenital abnormalities in epilepsy included cleft upper lip and hard palate, congenital cardiac defect (septal defect) and diaphragmatic hernia. This suggests that in epilepsy it is preferable to carry out monotherapy, despite the teratogenic effect of all drugs.

4. Conclusions

Epilepsy and the therapeutic regimen of antiepileptic drugs have a negative effect on pregnancy, causing various obstetric complications: preeclampsia (26.7%), fetoplacental insufficiency (46.7%), labor anomalies (22.2%), uterine subinvolution (15.6%). The criteria for assessing the degrees of compensation for epilepsy during pregnancy include: the group with a compensated form is patients whose pregnancy occurs against a background of fairly rare seizures or in remission on the background of drug therapy, the group with a subcompensated form is patients who have rare and sometimes frequent seizures during pregnancy, but on the background of antiepileptic therapy. There is a positive effect, the group with the decompensated form is patients with daily seizures., the lack of a positive effect even on the background of antiepileptic therapy. The incidence of complications during gestation is directly proportional to the degree of compensation for epilepsy and the parity of childbirth and does not depend on the type of epilepsy. Adverse outcomes in the perinatal period with compensation of epilepsy are observed in 30.43% of cases, that is, 2.8 times less than during the period of subcompensation of the disease (85.2%), and 3.3 times less than during the period of decompensation (100%). Women with compensated and subcompensated course need to undergo pre-emergency training and preventive therapy for AFN. During pregnancy, patients with epilepsy have primary early placental insufficiency, according to the results of analyses of placental as well as fetal hormones: a decrease in placental lactogen and estriol values from 12 to 25 weeks by 10-15% in absolute values compared with the control group, which indicates the presence of strains in the compensatory capabilities of adaptive systems.

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