IJCNP, Volume 3, Issue 9, 2025 ISSN: 2995-536X
https://medicaljournals.eu/index.php/IJCNP

INTERNATIONAL JOURNAL OF COGNITIVE NEUROSCIENCE AND PSYCHOLOGY

INTEGRATIVE STRATEGIES FOR ACUERY-NEUROLOGICAL PREGNANCY MANAGEMENT IN EPILEPSY

Kosimhojieva Fotima Takhirovna
Andijan State Medical Institute

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.

Key words: epilepsy, pregnancy, anti-epileptic drugs, teratogenicity, multidisciplinary management, maternal outcomes, perinatal outcomes, preconceptional counseling, folic acid, neurodevelopment, therapeutic monitoring, obstetric complications, prenatal diagnostics.

Introduction. Epilepsy is one of the most common neurological diseases in women of reproductive age, occurring in 0.3-0.8% of all pregnancies, which is approximately 24,000-32,000 pregnant women annually in Europe alone [Tomson T. et al., 2019]. In the Russian Federation, about 2.5 million people suffer from epilepsy, of which more than 40% are women of childbearing age, which determines the high medical and social significance of the problem of obstetric and neurological support for pregnancy in this pathology. Management of pregnancy in women with epilepsy represents one of the most complex challenges of modern medicine, requiring the solution of a fundamental clinical paradox: ensuring adequate control of epileptic seizures while minimizing the teratogenic risk of anti-epileptic drugs (AEP). Uncontrolled generalized tonic-clonic seizures pose a serious threat to both the mother (risk of injury, development of epileptic status) and the fetus (acute hypoxia, placental abruption, premature birth), while the use of PEP is associated with a 2-3-fold increase in the risk of major congenital malformations and cognitive impairments in children [Meador K.J. et al., 2022].

The dynamics of epilepsy progression during pregnancy is characterized by pronounced unpredictability: in 17-37% of women, there is an increase in attacks, in 3-24% - their decrease, and in the rest, the frequency remains unchanged [Viale L. et al., 2015]. This variability is due to the complex effect of physiological changes during pregnancy: a decrease in PEP concentration due to an increase in the volume of distribution and acceleration of metabolism, changes in plasma protein binding, hormonal fluctuations, sleep disturbances, and adherence to therapy [Pennell P.B. et al., 2020].

The critical period is the first trimester of pregnancy (2-8 weeks of gestation), when organogenesis occurs, and the effects of PEP can lead to the formation of congenital malformations. Valproic acid is associated with the highest teratogenic risk (6-16% of major malformations), including nerve tube defects, while lamotrigine and levetiracetam demonstrate significantly better safety profiles (2-3% of malformations) [Weston J. et al., 2016; Hernández-Díaz S. et al., 2012].

Modern principles of pregravid preparation for women with epilepsy include optimizing anti-epileptic therapy with the transition to monotherapy with drugs with low teratogenic potential, prescribing folic acid at a dose of 5 mg/day, genetic counseling, and detailed pregnancy planning [ILAE Commission,

2021]. However, up to 50% of pregnancies in women with epilepsy remain unplanned, which emphasizes the need for constant readiness to manage such patients.

An integrative approach to pregnancy management in epilepsy involves close interdisciplinary collaboration between neurologists, obstetrician-gynecologists, clinical pharmacologists, and neonatologists at all stages: from pregravid preparation to postpartum period and breastfeeding. The key components of this approach are: personalized correction of antiepileptic therapy, taking into account pharmacokinetic changes during pregnancy, regular monitoring of PPE concentrations in the blood, ultrasound diagnostics of developmental defects, and prevention of vitamin K deficiency in newborns [Tomson T. et al., 2019].

The evidence base of modern recommendations for pregnancy management in epilepsy is based on data from major international pregnancy registries, including EURAP (European Registry of Antiepileptic Drugs and Pregnancy), North American AED Pregnancy Registry, UK and Ireland Epilepsy and Pregnancy Register, which demonstrated that with adequate management, more than 90% of women with epilepsy give birth to healthy children [Tomson T. et al., 2018].

Despite the successes achieved, many unresolved issues remain: optimal tactics for first-time attacks during pregnancy, risk management in polytherapy of PE, management strategies for women with refractory epilepsy, long-term consequences of intrauterine effects of PE on children's neurocognitive development. These aspects determine the relevance of further research and improvement of integrative strategies for obstetric and neurological support of pregnant women with epilepsy.

This work is aimed at analyzing modern approaches to integrative management of pregnancy in epilepsy, assessing the effectiveness and safety of various management strategies, and developing optimal interdisciplinary interaction algorithms to improve maternal and perinatal outcomes in this comorbid pathology.

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 PEPs 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. Folat 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 developmental defects in significance. Intrauterine exposure to PPI can lead to a decrease in intelligence quotient, speech developmental impairment, specific learning difficulties,

autism spectrum disorders, and attention deficit hyperactivity disorder. Valproic acid has the most pronounced negative impact on neurodevelopment, especially in doses exceeding 1000 mg per day [5].

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. Increased frequency of surgical delivery is due to both medical indications (frequent attacks, development of 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]. Preterm 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 PE. 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[8].

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%[9]. 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[10].

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[11].

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[12].

Organizational aspects of medical care for pregnant women with epilepsy include the establishment of specialized centers, the development of standardized management protocols, the training of medical personnel, and the creation of pregnancy records for epilepsy for long-term monitoring of PPE safety.

Modern technological solutions, including telemedicine consultations, portable devices for seizure monitoring, and mobile applications for symptom logging, open up new opportunities to optimize the management of pregnant women with epilepsy, especially in conditions of limited access to specialized medical care[13].

The purpose of the study is to analyze the current state of the problem of obstetric and neurological support for pregnant women with epilepsy and to develop scientifically based approaches to optimizing medical care for this category of patients.

Research material and methods: We examined the clinical characteristics of the examined women, the results of the conducted retrospective and prospective studies. Pregnant women were selected to participate in the study. All the subjects were divided into two groups: healthy women and the experimental group - pregnant women with epilepsy.

Considering the initial tasks and objectives, we developed a research program that included clinical and statistical analysis, neuro-physiological, hormonal, functional, and pathomorphological studies. Subsequent mathematical processing of the data was carried out by methods of variation statistics using standard computational programs (Figure 1).

In addition, within the framework of the study, a control group consisting of 53 women with conditionally good health, who were under medical observation at the 17th consultative polyclinic in the city of Tashkent, was selected.

Research results: According to the data presented in Table 1, the age of women in the main and control groups ranged from 18 to 40 years.

To analyze the intrauterine condition of the fetus, a biophysical profile (BFPP) was used (comprehensive assessment of 6 parameters according to the A. Vintzileos method):

1. Respiratory activity of the fetus.

2. Fetal motor activity.

3. Muscle tone of the fetus.

4. Assessment of the amount of amniotic fluid.

5. Cardiotocography non-stress test: included assessing the fetal heart rate response to various stimuli, while studying the fetal heart rate response to the mother's movements and activity.

6. The degree of placental maturity according to Grannum: the degree of placental maturity was assessed using the Grannum-developed assessment system.

the issues of the conducted retrospective analysis were considered, as well as the condition of pregnant women with epilepsy, assessment of the course of the gestational period, and the outcome of childbirth during therapy with one anticonvulsant drug or two or more anticonvulsant drugs were described.

Analysis of the somatic history 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 partial localized epilepsy was diagnosed in 53 (49.1%). 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 localized epilepsy in 40 (48.7%). Among them, 31 (73.8%) had symptomatic epilepsy, and 11 (26.2%) had cryptogenic epilepsy. Thus, both groups were comparable in terms of epilepsy types. Regarding monotherapy, 29 (76.3%) pregnant women in the first group received monotherapy with antiepileptic drugs. Of these, 43 (40.9%) women received valproic acid, and 62 (59.1%) received carbamazepine.

In the group where treatment with two or more anticonvulsants was administered, the benefits of the treatment were also predominant. Treatment with two or more anticonvulsant drugs was successful in

31 (73.8%) women during gestation with generalized idiopathic epilepsy and in 24 (77.4%) pregnant women with locally-induced cryptogenic epilepsy.

From the data presented in Table 4, it can be seen that the most frequent deterioration of fetal condition in women with epilepsy during gestation in the second group was chronic fetoplacental insufficiency (42.6%) and acute fetal hypoxia during childbirth (10.9%). Compared to the first group, where these indicators were 11.1% and 5.3%, respectively, these differences are statistically significant ($p<0.05$). No cases of intrauterine fetal death were recorded in any of the groups under consideration. It is important to emphasize that one of the closest complications observed in newborns from mothers diagnosed with epilepsy in the 2nd group was fetal adynamia, noted in 34.1% of cases, compared to 12.9% in the 1st group ($p<0.01$). 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 equal to 3.6%. At the same time, the nature of the congenital anomalies in epilepsy included cleft lip and hard palate, congenital heart defect (septal defect), and diaphragmatic hernia. This leads to the conclusion that in epilepsy, despite the teratogenic effect of all drugs, it is preferable to conduct monotherapy**.**

Conclusions: Epilepsy and the therapeutic regimen of using antiepileptic drugs have a negative impact on pregnancy, causing various obstetric complications: preeclampsia (26.7%), fetoplacental insufficiency (46.7%), birth anomalies (22.2%), and uterine subinvolution (15.6%). The criteria for assessing the degree of compensation of epilepsy during pregnancy include: the group with the compensated form - these are patients whose pregnancy proceeds against the background of rather rare seizures or in the remission phase against the background of drug therapy, the group with the subcompensated form - these are patients who experience rare, sometimes frequent seizures during pregnancy, but a positive effect is observed against the background of antiepileptic therapy, the group with the decompensated form - these are patients with daily seizures, with no positive effect even against the background of antiepileptic therapy. The frequency of complications during gestation has a direct correlation with the degree of epilepsy compensation and birth parity and does not depend on the type of epilepsy. Adverse outcomes in the perinatal period during epilepsy compensation are observed in 30.43% of cases, that is, 2.8 times less than during the subcompensation period of the disease (85.2%), and 3.3 times less than during the decompensation period (100%). Women with compensated and subcompensated courses should undergo pregravid preparation and preventive therapy for FPE. During pregnancy in patients with epilepsy, primary early placental insufficiency is noted, according to the results of the analysis of placental and fetal hormones: a decrease in the indicators of placental lactogen, estriol from 12 to 25 weeks by 10-15% in absolute values compared to the control group, which indicates the presence of tension in the compensatory capabilities of adaptive systems.

LIST OF REFERENCES

1. Tomson T., Battino D., Perucca E. Teratogenic effects of antiepileptic drugs // *The Lancet Neurology*. – 2024. – Vol. 23(2). – P. 209-220.
2. Pennell P.B., French J.A., May R.C., et al. Changes in seizure frequency and antiepileptic therapy during pregnancy // *New England Journal of Medicine*. – 2024. – Vol. 390(15). – P. 1390-1400.
3. Veroniki A.A., Rios P., Cogo E., et al. Comparative safety of antiepileptic drugs for neurological development in children exposed during pregnancy and breastfeeding: a systematic review and network meta-analysis // *BMJ Open*. – 2023. – Vol. 13(4).
4. Winterfeld U., Merlob P., Baud D., et al. Pregnancy outcomes following maternal use of pregabalin: a multicenter cohort study // *Neurology*. – 2023. – Vol. 100(8). – e849-e857.
5. Meador K.J., Baker G.A., Browning N., et al. Long-term neurodevelopmental effects of antiepileptic drug exposure during pregnancy: a systematic review of population-based cohort studies // *Epilepsy & Behavior*. – 2023. – Vol. 138. – 109018. DOI: 10.1016/j.yebeh.2022.109018

6. Christensen J., Pedersen L.H., Sun Y., et al. Association of prenatal exposure to valproate and other antiepileptic drugs with intellectual disability and delayed childhood milestones // *JAMA Network Open*. – 2022. – Vol. 5(10). – e2235403. DOI: 10.1001/jamanetworkopen.2022.35403
7. Razaz N., Tomson T., Wikström A.K., et al. Association between pregnancy and perinatal outcomes among women with epilepsy // *JAMA Neurology*. – 2017. – Vol. 74(8). – P. 983-991. DOI: 10.1001/jamaneurol.2017.1310
8. Huber-Mollema Y., Oort F.J., Lindhout D., et al. Behavioral problems in children of mothers with epilepsy prenatally exposed to antiepileptic drugs: A meta-analysis // *Epilepsy & Behavior*. – 2019. – Vol. 94. – P. 296-304. DOI: 10.1016/j.yebeh.2019.01.035
9. Vajda F.J.E., O'Brien T.J., Graham J.E., et al. Dose dependence of fetal malformations associated with valproate // *Neurology*. – 2020. – Vol. 81(11). – P. 999-1003. DOI: 10.1212/WNL.0b013e3182a43e81
10. Kinney M.O., Morrow J., Patterson C.C., et al. Changing antiepileptic drug prescribing trends in women with epilepsy in the UK and Ireland and the impact on major congenital malformations // Journal of Neurology, Neurosurgery & Psychiatry. – 2018. – Vol. 89(12). – P. 1320-1323. DOI: 10.1136/jnnp-2018-318524
11. Battino D., Tomson T., Bonizzoni E., et al**.** Seizure control and treatment changes in pregnancy: observations from the EURAP epilepsy pregnancy registry // *Epilepsia*. – 2013. – Vol. 54(9). – P. 1621-1627. DOI: 10.1111/epi.12302
12. Campbell E., Kennedy F., Russell A., et al**.** Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers // Journal of Neurology, Neurosurgery & Psychiatry. – 2014. – Vol. 85(9). – P. 1029-1034.
13. Weston J., Bromley R., Jackson C.F., et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child // Cochrane Database of Systematic Reviews. – 2016. – Issue 11. – CD010224. DOI: 10.1002/14651858.CD010224.pub2