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CLINICAL AND PHARMACOLOGICAL CONTROL IN THE COMPREHENSIVE DIAGNOSIS OF EPILEPTIC DISORDERS IN WOMEN DURING PREGNANCY

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Abstract: Epilepsy is one of the most common neurological diseases, occurring in 0.5-1% of the population, with approximately 40% of patients being women of reproductive age. Managing pregnant women with epilepsy is a complex clinical task that requires balancing between managing maternal epileptic seizures and minimizing the risks to the developing fetus.

Keywords: epilepsy, pregnant women, clinical recommendations, reproductive age, neurology

Introduction. Physiological changes occurring in a woman's body during pregnancy significantly affect the pharmacokinetic parameters of anti-epileptic drugs (AEP). Increased circulating plasma volume, changes in plasma protein binding, increased hepatic metabolism, and renal excretion lead to a decrease in the concentration of free drug fractions in blood serum, which can lead to increased attacks even with standard doses. The complexity of the problem is exacerbated by the need to consider the teratogenic potential of PPE, their influence on the course of pregnancy and fetal development. Modern studies indicate an increased risk of congenital developmental anomalies, intrauterine developmental delays, and neurological disorders in children whose mothers received antiepileptic therapy during pregnancy. Therapeutic drug monitoring (TMM) in epilepsy obstetrics is of particular importance, as it allows for the optimization of drug dosages, taking into account individual pharmacokinetic characteristics and physiological changes during the gestational period. Controlling the concentration of PEP in blood plasma ensures the maintenance of therapeutic levels necessary to prevent attacks, while simultaneously reducing the risk of toxic effects. A multidisciplinary approach to diagnosing and managing pregnant women with epilepsy involves close collaboration between neurologists, obstetrician-gynecologists, clinical pharmacologists, geneticists, and neonatologists. The integration of clinical data, electroencephalography results, neuroimaging, and pharmacokinetic studies allows for a personalized approach to therapy. Differential diagnosis of epileptic and non-epileptic paroxysmal conditions during pregnancy requires special attention, as gestational changes can modify the clinical picture of seizures. Hormonal fluctuations, changes in electrolyte balance, stress, and sleep disturbances can trigger both true epileptic seizures and psychogenic non-epileptic events.

Modern algorithms for managing pregnant women with epilepsy are based on the principles of evidence-based medicine and include regular monitoring of PEP concentration, dose adjustment considering the pregnancy trimester, prevention of folic acid and vitamin D deficiency, and planning childbirth with minimal risk of birth attacks.

The development of modern analytical methods, including highly effective liquid chromatography and mass spectrometry, provides the ability to accurately determine the concentration of both traditional and new PEPs, which expands the possibilities of personalized therapy. This study is aimed at systematizing modern approaches to clinical and pharmacological monitoring of epilepsy in pregnant women, assessing the effectiveness of various monitoring strategies, and developing optimal algorithms for managing patients to improve maternal and perinatal outcomes.

The purpose of the study is to analyze the diagnostic and clinical aspects of pregnancy management in women with epilepsy within the framework of a multidisciplinary approach.

Research material and methods. The study included pregnant women with an established diagnosis of epilepsy who were under dynamic observation in outpatient and inpatient settings of the Multidisciplinary Clinic of Samarkand State Medical University (neurology department, obstetrics and gynecology department, women's consultation at the MS SamSMU polyclinic), as well as in specialized obstetric institutions of the city of Samarkand. The total number of examined patients was n=48 pregnant women aged 19 to 38 (average age - 27.6±4.9), who were observed at different gestational ages during the period 2023-2025, constituting the main group of examined patients.

The study group consisted of 29 (60.4%) patients with more than 5 years of epilepsy experience, while the duration of the disease less than 5 years was noted in 19 (39.6%) patients. By type of epilepsy, the following were represented: focal forms in 31 patients (64.6%), generalized forms in 17 patients (35.4%).

The inclusion criteria in the study were: the presence of a clinical diagnosis of epilepsy according to ICD-10 (G40), pregnancy regardless of gestational age, age from 18 to 40, as well as the presence of the patient's informed written consent to participate in the study. The criteria for exclusion were: epileptic status in the anamnesis less than 6 months before inclusion in the study, severe somatic pathology in the decompensation stage, pronounced mental disorders, active infectious diseases, oncological pathology, as well as the patient's refusal to participate in the study.

Depending on the clinical and diagnostic characteristics, the patients were further distributed according to a number of criteria. According to the frequency of seizures during pregnancy, groups were distinguished: without seizures - 21 patients (43.8%), rare seizures - 17 (35.4%), frequent seizures - 10 (20.8%). By trimester of pregnancy: I trimester 14 patients (29.2%), II trimester 18 (37.5%), III trimester 16 (33.3%).

The control group for comparative analysis consisted of 30 pregnant women comparable in age and gestational age, without epilepsy and other chronic neurological diseases, who underwent planned monitoring at the women's consultation.

All pregnant women in the main and control groups underwent a comprehensive clinical and diagnostic examination within the multidisciplinary approach with the participation of a neurologist, obstetrician-gynecologist, and, if necessary, a therapist and neonatologist. The examination was carried out in stages, taking into account the gestational age and clinical and neurological features of the course of epilepsy. Neurological examination included assessing the history of the disease, the type of epilepsy, the duration of the disease, the frequency and nature of seizures before and during pregnancy, as well as the analysis of possible triggering factors. A dynamic assessment of the neurological status was conducted with the fixation of non-motor symptoms and signs of neurovegetative instability. Obstetric and gynecological examination included assessing the course of pregnancy, ultrasound monitoring data, the condition of uteroplacental blood flow, as well as identifying obstetric risk factors capable of influencing the course of epilepsy and fetal condition. Particular attention was paid to gestational age, the presence of pregnancy complications, and the peculiarities of the perinatal history. Within the framework of laboratory and instrumental diagnostics, standard clinical and laboratory methods, electroencephalography (EEG) during the inter-attack period, as well as functional assessment of the central nervous system during dynamic observation, were used. The obtained data were analyzed in conjunction with clinical indicators. As a key methodological element of the study, a

multidisciplinary diagnostic algorithm for monitoring pregnant women with epilepsy was developed and applied, based on the integration of neurological, obstetric-gynecological, and functional examination data. The algorithm included a sequential assessment of: clinical and neurological characteristics of epilepsy; features of pregnancy progression and obstetric risk factors; EEG data and functional state of the central nervous system; dynamic interdisciplinary discussion of the patient's observation tactics. The application of this algorithm made it possible to systematize the diagnostic process, increase the detection of risk factors for an unfavorable course of pregnancy, and ensure a unified approach to interdisciplinary interaction in the observation of pregnant women with epilepsy.

Therapeutic drug monitoring (TDM) of antiepileptic drugs was used as an innovative diagnostic element of the study. Determination of the concentration of anti-epileptic drugs in blood serum was carried out in the dynamics of pregnancy (by trimesters) using standardized laboratory methods. The obtained levels of antiepileptic drugs were analyzed, taking into account gestational age, the type of epilepsy, and the clinical frequency of seizures. Laboratory indicators were compared with clinical and neurological data, electroencephalographic examination results, and obstetric parameters, which made it possible to assess the individual characteristics of pharmacokinetic changes in antiepileptic drugs during pregnancy. The use of therapeutic drug monitoring was considered as an additional diagnostic tool that allows for the objectification of the risk of destabilization of the epileptic process and increases the accuracy of multidisciplinary monitoring of pregnant women with epilepsy.

Statistical processing of the obtained data was carried out using Statistica and SPSS application software packages on an individual computer. Quantitative indicators are presented as average values and standard deviation. For intergroup comparison, parametric and non-parametric statistical analysis methods were used depending on the nature of data distribution, including Mann-Whitney's U-criterion and Pearson's $\chi 2$. Correlation analysis was performed using Spearman's coefficient. Differences were considered statistically significant at a level of $p < 0.05$.

Research results. By studying the results of a comprehensive clinical and diagnostic examination of pregnant women with epilepsy, it was revealed that the course of the disease during pregnancy is characterized by pronounced individual variability, caused by a combination of clinical, obstetric, and pharmacokinetic factors. The use of a multidisciplinary approach, including therapeutic drug monitoring, allowed for the identification of significant diagnostic patterns inaccessible under standard clinical observation. Thus, according to clinical and neurological examination data, the course of epilepsy during pregnancy remained stable in 27 patients (56.3%), while in 21 women (43.7%), there was an increase in seizures or the appearance of new types of paroxysms. These changes were registered significantly more frequently in the II-III trimesters of pregnancy ($p < 0.05$).

The results of therapeutic drug monitoring demonstrated a significant decrease in the concentration of anti-epileptic drugs in blood serum as gestational age increases. In the first trimester, a decrease in PEP levels below the individual therapeutic range was observed in 9 patients (18.8%), in the second trimester in 17 patients (35.4%), and in the third trimester in 26 patients (54.2%) ($p<0.001$). The most pronounced changes in pharmacokinetics were observed in patients receiving lamotrigine and levetiracetam.

A significant association has been established between the decrease in serum concentrations of anti-epileptic drugs and the clinical destabilization of the epileptic process. In patients with PEP levels below the individual therapeutic range, the frequency of seizures was noted in 68.2% of cases, while with the preservation of therapeutic concentrations, only in 21.7% of cases ($p<0.01$). These results confirm the diagnostic significance of laboratory monitoring as an early risk marker for the deterioration of the clinical course of epilepsy during pregnancy.

Comparison of laboratory data with the results of electroencephalographic studies showed that in patients with reduced PEP levels, an increase in epileptiform activity on EEG was registered significantly more often (61.5% versus 26.1%, $p<0.05$), which emphasizes the relationship between pharmacokinetic changes and the functional state of the central nervous system.

Based on the obtained data, a multidisciplinary diagnostic algorithm for monitoring pregnant women with epilepsy was developed, including the sequential integration of clinical, laboratory, and instrumental indicators. Where, at the first stage, a clinical and neurological assessment was conducted, analyzing the type of epilepsy, the frequency of attacks, and the dynamics of the neurological status. The second stage included obstetric and gynecological assessment of pregnancy and identification of gestational-dependent risk factors. The third stage was a laboratory block with determination of the concentration of anti-epileptic drugs in blood serum in dynamics over three months. The fourth stage included comparison of laboratory indicators with clinical data and EEG results within the framework of an interdisciplinary consultation.

The use of this algorithm made it possible to timely identify patients in groups with an increased diagnostic risk of destabilization of the epileptic process, even with the absence of pronounced clinical changes at the time of examination. Thus, laboratory monitoring of antiepileptic drugs has become a key element of multidisciplinary diagnostics, providing a more accurate and personalized assessment of the course of epilepsy during pregnancy.

The conducted correlation analysis revealed significant relationships between the decrease in the concentration of anti-epileptic drugs in blood serum and the clinical destabilization of the epileptic process in pregnant women. A pronounced inverse correlation was established between the level of PEP and the frequency of seizures ($r=-0.68$; $p<0.001$), as well as between the concentration of PEP and the severity of epileptiform activity on EEG ($r=-0.61$; $p=0.002$). Furthermore, a direct correlation was found between the frequency of seizures and increased epileptiform activity on EEG ($r=0.57$; $p=0.004$), confirming the diagnostic significance of a comprehensive assessment of clinical and instrumental indicators. A strong negative correlation was noted between gestational age and PEP concentration ($r=-0.72$; $p<0.001$), indicating progressive pharmacokinetic changes in anti-epileptic therapy during pregnancy.

Conclusions

1. The course of epilepsy in pregnant women is characterized by progressive pharmacokinetic changes in antiepileptic drugs, manifested by a significant decrease in their serum concentrations as gestational age increases, making laboratory monitoring an objective diagnostic marker of the risk of clinical destabilization of the disease.
2. The identified reliable correlations between the decreases in the level of antiepileptic drugs, the frequency of seizures, and the increase in epileptiform activity on EEG confirm the diagnostic significance of integrating laboratory, clinical, and instrumental indicators in the observation of pregnant women with epilepsy.
3. The use of a multidisciplinary diagnostic algorithm, including therapeutic drug monitoring of antiepileptic drugs, provides a more accurate and personalized assessment of the course of epilepsy during pregnancy and represents a methodologically new approach to the diagnosis and monitoring of this category of patients.

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