Pregnancy and epilepsy: focus on seizure frequency changes and obstetric complications. Progress in studies and lag in practice

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Epilepsy is a common neurological disease that negatively affects all areas of life, with a need to take antiepileptic drugs (AEDs) for a long time and with a high incidence of side effects.
Objective: *to determine the main directions of studies dealing with the problem of pregnancy in epilepsy, by analyzing their results.*
Material and methods. *Over past 10-year publications on pregnancy in epilepsy, their prospects for and prognostic significance for solving scientific and practical problems underwent an analytical review.*
Results and discussion. *It was found that the risk for higher frequency of seizures was 15 times lower if the latter were controlled within 9–12 months before pregnancy. AED therapy noncompliance during pregnancy is the cause of relapses, increased seizure frequency, and status epilepticus. Changes in the blood concentrations of AED during pregnancy require therapeutic drug monitoring and correction of daily dosages of these drugs. The indication for caesarean section in epilepsy is a high perinatal and maternal risk. Breastfeeding in maternal epilepsy is indicated applying a personalized approach. Studying the predictors of changes in the frequency of seizures and improving pregravid preparation are promising areas for optimizing pregnancy outcomes in epilepsy.*

Keywords: *epilepsy; women; pregnancy; seizures; status epilepticus; cesarean section; antiepileptic drugs.*
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Abbreviations: AEDs – antiepileptic drugs, CBZ – carbamazepine, DRE – drug-resistant epilepsy, ESM – ethosuximide, GBP – gabapentin, HMD – hexamidin, IGE – idiopathic generalized epilepsy, LTG – lamotrigine, OXZ – oxcarbazepine, PB – phenobarbital, PT – phenytoin, SE – status epilepticus, TPM – topiramate, VPA – valproic acid, WHO – World Health Organization, EURAP – European Registry of Antiepileptic Drugs and Pregnancy

Epilepsy became an issue of global importance after the WHO report entitled TEPILEPSY: a public health imperativeУ in 2019 [1]. Epilepsy in women is associated with a high percentage of reproductive losses, low fertility, risk of fetal malformations, and neurobehavioural teratogenicity [4]. Clinical investigations of newer AED effects on the developing fetus are prohibited worldwide for ethical issues [2]. However, meta-analyses are often complicated by methodological differences in material collection.

In 2009 the AAN published specific guidelines for the appropriate management of women with epilepsy, with a particular focus on pregnancy [5, 6]. However, over the past 10 years, there have been significant advances in epileptology and pharmacotherapy for epilepsy, newer AEDs have been introduced. In 2019 the ERAP published data on the risks for the fetus associated with maternal epilepsy [7].

For example, a search of the Web of Science using the keywords "epilepsy" and "pregnancy" demonstrated that more than 600 papers were published per year. The focus was on the analysis of publications on the course of epilepsy in pregnant women, primarily on the changes in the frequency of epileptic seizures.

Issues related to pregnant women with epilepsy appear relevant, as the most important issues of epilepsy management during pregnancy have not been analysed in randomized clinical trials, which are the gold standard of evidence-based medicine. This lack of evidence base inevitably leads to the need for systematic reviews of the main trends and research results of the problem of pregnancy in women with epilepsy.

The **OBJECTIVE** of this study is to determine the main directions of research on pregnancy in epilepsy, including the analysis of research results as well as their prospects and prognostic value based on a systematic analytical review of publications on epilepsy and pregnancy from 2009–2020 with an emphasis on Russian research.

MATERIALS AND METHODS

Description of analytical process

The study design was a retrospective observational study. The research team included researchers and physicians (neurologists and epileptologists).

Literature review and selection of articles

The subject of research was scientific papers on pregnancy in women with epilepsy. A literature search was performed in global and local databases (e-library, PubMed, Scopus, Web of Science) from 2009 through 2020. The primary analysis included 200 publications; abstracts and experimental animal testing were excluded from further analysis. For a full review we selected 50

articles devoted to pregnancy in women with epilepsy based on the originality and scope of the studies, focused on two main topics: changes in the frequency of epileptic seizures and complications of pregnancy associated with epilepsy. We should note an increased number of publications on pregnancy in women with epilepsy in comparison with the data from 2009.

I. COURSE OF EPILEPSY DURING PREGNANCY

1) Change in the frequency of epileptic seizures

One of the most important issues associated with women with epilepsy is the impact of pregnancy on the course of epilepsy. In 2017 the Russian Registry of Pregnancy and Epilepsy (RRPE) was launched in the Russian Federation [8]. Seizure frequency control during pregnancy differs according to the authors' data. According to Thomas S.V. et al, of 1,297 pregnant women, 47.8% had complete control over epileptic seizures during pregnancy. [9]. In the study by Magalov Sh. et al. including 96 patients, 32% of pregnant women had no epileptic seizures, 72% experienced seizures during pregnancy and 16% had no change in seizure frequency [10]. The EURAP data showed the dynamics of epileptic seizure control throughout pregnancy from 58.3% in 2006 to 66.6% in 2013, whereas seizure frequency increased in 15.8%, and did not change in 70.5% of cases [11]. Thus, control of epileptic seizures during pregnancy varies from 32% to 66.6%.

2) Recurrent seizures and new onset epilepsy during pregnancy

Recurrent seizures occur more often than new onset epilepsy during pregnancy. Recurrent seizures occurred in 25% of cases [12]. New onset epilepsy during pregnancy is described in 2.1% [17]. New onset epilepsy during pregnancy in a cohort of 1041 women was recorded in 11.4% of cases [18]. New onset epilepsy during pregnancy ranges from 2.1% to 11.4%, and recurrent seizures are recorded in 25% of women.

3) The effect of the form of epilepsy on changes in the frequency of epileptic seizures during pregnancy

Pregnant women with epilepsy have a fairly high proportion of IGE [19]. 73.2% of women with IGE had no increase in the seizure frequency during pregnancy, and deterioration of epilepsy occurred in 27% [20]. According to Dmitrenko D.V, 77.7% of women with IGE had no epileptic seizures during pregnancy, and the predominant seizure type was IGE – 47.1% ($p < 0.01$) [12]. Women with IGE were more likely to have no epileptic seizures (73.6%) than women with focal epilepsy (59.5%; $p < 0.0001$) [11]. Pregnant women with focal epilepsy had no epileptic seizures in 26.3% of cases, increased frequency was noted in 33.3%, no change in frequency was found in 14.1%; in women with IGE – 43%, 14.2% and 21.4%, respectively [10]. Seizure deterioration in pregnancy is more frequent in women with focal epilepsy than in women with idiopathic generalized epilepsy [21]. Overall, 43% to 77.7% of women with idiopathic generalized epilepsy did not have epileptic seizures during pregnancy.

4) Aeds and changes in seizure frequency during pregnancy

Risks of uncontrolled seizures during pregnancy should be balanced against the potential teratogenic effects of AEDs. The effect of AED type on epilepsy course during pregnancy was demonstrated in 2009 when studying seizure frequency against the background of Lamotrigine monotherapy during pregnancy; increased seizure frequency was found in 19% of 42 women [22]. The data obtained from the Australian Pregnancy Register confirmed the efficacy of Levetiracetam in controlling seizures in pregnant patients [23]. Pregnancy can influence AED pharmacokinetics at any level, depending on the type of medication [24] due to alterations in their clearance and distribution [25]. Thus, a decrease in concentrations of Lamotrigine, Levetiracetamum, the active metabolite of Oxcarbazepine, Topiramate, and Zonisamide was observed in pregnant patients. Early therapeutic drug monitoring and dose adjustment can help prevent increased seizure frequency [26,27].

Clinical deterioration occurred in 70.6% of 51 women who switched from VPA to other drugs (28). Adverse reactions while using VPA were more often registered in heterozygous carriers of single nucleotide polymorphisms of CYP2C9*3 (27.3%) [29]. The most common AEDs used as monotherapy in the USA in 2018 were Lamotrigine (42.1%), Levetiracetam (37.5%), Carbamazepine (5.4%), Zonisamide (5.0%), Oxcarbazepine (4.6%), and Topiramate (3.1%) [30]. Pregnant women treated with polytherapy are less likely to avoid seizures than those managed with monotherapy, both with focal epilepsy and IGE. The safety of vagus nerve stimulation during pregnancy has not been adequately studied [31]. It is important to aim for the lowest effective doses of AEDs at conception and during early pregnancy; more attention should be paid to dose adjustment during pregnancy to improve the outcome [11].

5) Seizure worsening DURING PREGNANCY and its predictors

According to the AAN in 2009, if women had no seizures from 9 months to 1 year before pregnancy, the control of seizure frequency during pregnancy was up to 84–92% [6]. The following is the most significant factor associated with an increased seizure frequency in cases of IGE: seizure frequency more than once a year. Interictal epileptiform discharges positively correlated with increased seizure frequency during pregnancy ($r = 0.76$; $p = 0.00001$) [20]. Seizures one month before pregnancy continue during pregnancy in 91.9% of cases, but if seizures are absent during this month, they occur in pregnancy only in 42.9% of cases. Women who had seizures one month before pregnancy had 15 times higher risk of seizures during pregnancy ($p = 0.001$) [32]. In 18.7% of pregnant women with epilepsy, the dose of antiepileptic drugs was self-changed or changed by an obstetrician-gynaecologist, which caused an increased number of seizures [12]. Disruption of normal daily routine, sleep deprivation, and non-compliance with drug therapy led to worsening of the course of epilepsy during pregnancy [18]. A predictive model was published for determining the risk of seizures during pregnancy and up to 6 weeks postpartum in women with epilepsy managed with AEDs, based on the data from a prospective cohort study (EMPiRE) of 527 pregnant women with epilepsy taking AEDs [33]. More than 90% of women with epilepsy can expect a favourable pregnancy and delivery outcomes [34].

CONCLUSIONS

1. The risk of increased frequency of seizures is 15 times lower when seizures are taken under control 9–12 months before pregnancy.
2. Seizure control during pregnancy is more common in IGE than in FE.
3. Poor compliance with AED therapy during pregnancy is a common cause of recurrent seizures, increased seizure frequency, and SE during pregnancy.
4. Changes in AED blood concentrations during pregnancy require therapeutic drug monitoring and adjustment of daily doses of AED.

II. EPILEPSY DURING PREGNANCY

1) Pregnancy complications

A total of 55% of pregnancies among women with epilepsy are unplanned compared to 48% in healthy women [35]. However, there can be direct damage to the fetus, fetal hypoxia caused by generalized epileptic seizures, and intrauterine fetal death in cases of SE [36]. The most common complications of pregnancy and childbirth in women with epilepsy were anaemia, a threat of spontaneous abortion, placental insufficiency, preeclampsia, and premature birth [37]. The most frequent reasons for hospitalization were placental insufficiency (13.2%), threatened abortion (27.9%), oedema (29.5%), and moderate preeclampsia (1.6%) [38].

Epilepsy was identified as a significant risk factor for premature birth, C-section, fetal hypoxia, and Apgar scores I 7 at 5 minutes [39]. Recent studies revealed the following among women with epilepsy: increased rate of induced labour ($p < 0.005$), the use of epidural analgesia ($p < 0.005$), decreased mild preeclampsia ($p = 0.006$), increased risk of severe preeclampsia, increased use of folic acid, and decreased smoking during pregnancy ($p < 0.005$) [40].

2) Childbirth and C-Section

The frequency of abdominal delivery in pregnant women with epilepsy was 21%, and extragenital pathology was the main indication for C-section [41]. A total of 4.3% of deliveries were premature, and 73.33% were normal vaginal deliveries [43]. In total, 5.7% of women with epilepsy experienced premature delivery while they were on polytherapy; full-term babies were born in 94.3% of cases [44]. High perinatal and maternal risks are indications for C-section [42].

3) Teratogenesis and healthy generation

The prevalence of malformations during monotherapy decreased from 6.0% in 2000–2005 to 4.4% in 2010–2013 [50]. Mechanisms of teratogenicity of VPA include the inhibition of histone deacetylase, oxidative stress, certain folate antagonists, impaired expression of transporter proteins with subsequent increase in the content and accumulation of AEDs in fetal tissues [49]. There is a unanimous opinion on the necessity of folic acid use in the first trimester of pregnancy in women with epilepsy [47]. The birth rate of newborns with IUGR I–II was 20%; 85% of newborns were born with an Apgar score of 8 in the first minute [45]. Infants of mothers with epilepsy were more likely to have minor developmental anomalies and mild hypotrophy [46]. In the residual period, 71.1% of babies had significant motor and cognitive disorders, and 13.3% developed epilepsy [34]. Lamotrigine, Phenobarbital, Pregabalinum, Primidonum, Tiagabinum, Eslicarbazepinum Brivaracetamum, Perampanelum, Zonisamidum, Lacosamidum, or sporadic use of low-dose benzodiazepines are considered to be safe during breastfeeding [48]. The decision on breastfeeding should be made by taking into account AED type, amount, dose, serum level, transmission and elimination rates in infants, and the condition of the newborn.

Considerations

1. Pregnancy planning and preparation for pregnancy are high-potential methods of reducing pregnancy complications in patients with epilepsy.
2. Using the lowest effective doses of AEDs during conception and early pregnancy and adjusting the dosage during pregnancy cut the risk of teratogenic effects and improve outcomes.
3. Indications for C-section in women with epilepsy include high perinatal and maternal risks.
4. Breastfeeding is indicated for mothers with epilepsy in the case of a personalized approach to treatment.

DISCUSSION

Thus, a review of studies on the impact of epilepsy on pregnancy with a focus on changes in seizure frequency and obstetric complications confirmed the relevance and versatility of the problem. New possibilities for research of pharmacotherapy of epilepsy are being actively expanded, due to the introduction of the newer antiepileptic drugs into practice [52]. This determines a set of changes in the use of AEDs during pregnancy, the study of the impact of newer AEDs on seizure frequency [30]. The launching of the Russian Pregnancy and Epilepsy Register promotes changes in the spectrum of AEDs prescribed for women with epilepsy during pregnancy [8]. The focus is maintained on the study of predictors of changes in seizure frequency during pregnancy; further research needs to be conducted in this area [32, 33].

Recent studies of pregnancy in epilepsy have become more cross-functional and interdisciplinary, and actively assimilate a range of methods of natural and humanitarian sciences (neurophysiology, neurobiology, molecular, behavioural genetics, cognitive science, linguistics, informatics, and others) [29, 49]. Pregnancy complications in women with epilepsy are actively studied by obstetricians and gynaecologists [36, 38]. Infertility in epilepsy is an indication for the use of assisted reproductive technologies [51]. Women with epilepsy planning a pregnancy need a complex preconception preparation. The Russian Antiepileptic League, along with international organizations, informed the professional medical community about the effects of VPA during pregnancy and about the necessary measures to prevent them [54]. The study of the effects of epilepsy and AED on the development of offspring has become more comprehensive and is not restricted to researching only teratogenic effects of AED [39, 43, 44]. The focus of scientific attention is on the impact of epilepsy and AEDs on the fetal growth and prenatal as well as newborn's physical development [7, 46], and breastfeeding policy [35, 48]. Scientific debates on neurobehavioural teratogenicity of old and new generation AEDs remain active [7, 49].

Seizures during pregnancy are a complex public health and pharmacogenetic problem and should be examined thoroughly [53, 54]. Pharmacogenetic testing is actively used in clinical practice [29].

CONCLUSIONS

Comprehensive study on the fundamental mechanisms of reproductive health and disorders is one of the most important interdisciplinary scientific tasks of special social significance.

Systematic reviews can help practicing physicians address specific practical issues.

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