Epilepsy and pregnancy

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There are currently about 15 million women of childbearing age worldwide who suffer from epilepsy. Overall, 0.3–0.4% of newborns are born to mothers with epilepsy, and almost half of these women experience recurrent seizures. The article discusses issues related to pregnancy planning, the prognostic impact of seizure frequency, type and course of epilepsy on pregnancy outcomes, and potential risks associated with this condition. Summarized data from the latest recommendations for correction of therapy and data on changes in the pharmacokinetics of antiepileptic drugs during pregnancy are presented. A classification of antiepileptic drugs according to their teratogenic potential and their effect on the development and behaviour of the child is presented. Various approaches to pregnancy management are discussed. In addition, scenarios for pregnancy management in poorly controlled epilepsy and status epilepticus are discussed as well as adjustment of therapy in the postpartum period and measures for the safe care of newborns.

Keywords: *epilepsy; pregnancy; pregnancy planning; pregnancy management; anticonvulsants; postpartum period; teratogenesis; major congenital malformations.*

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Currently, there are about 15 million women of childbearing age worldwide who suffer from epilepsy [1]. The prevalence of epilepsy among pregnant women is 0.33–0.49% [2, 3]. Annually, about 0.3–0.4% of newborns are born to mothers with epilepsy, and the increased effectiveness of epilepsy therapy over the past 20 years with the use of new antiepileptic drugs (AEDs) has led to a fourfold increase in the number of pregnancies in women with epilepsy [4].

Dynamics of seizure frequency during pregnancy

According to several studies, when patients have been in remission for ⩾9 months before conception, there is hope for the absence of seizures during pregnancy [5].

In a prospective observational multicenter cohort study by P.B. Pennell et al. [6], the frequency of seizures during pregnancy and the first 6 weeks postpartum (observation period I) was compared with the frequency in the postpartum period (the following 7.5 months after pregnancy; period II) in 299 women. The control group (n=93) consisted of non-pregnant women with epilepsy. Unchanged frequency, an increase and decrease in seizures with impaired consciousness in both pregnant and non-pregnant women were almost identical: unchanged frequency – 63% in pregnant and 65% in non-pregnant women, a decrease – in 14% and 11% of cases, respectively; an increase – in 23% and 25%.

According to the results of the largest study EURAP (3806 pregnancies), the absence of seizures during pregnancy was observed in 66.6% of cases. For idiopathic generalized epilepsy (IGE), the rate was 73.6%, and for focal epilepsy (FE) – 59.5% [7]. There were 21 cases of status epilepticus (10 of them convulsive): none with maternal mortality and only one case of stillbirth [7].

In a single-center study (114 pregnancies) by P.E. Voinescu et al. [8], a clear dependence of the more benign course of IGE during pregnancy and non-frontal FE was revealed, especially when seizure control was achieved before pregnancy for a 9-month period. A more detailed analysis of the results revealed that patients with frontal epilepsy experienced an increase in seizures during pregnancy (75%) when seizure control was not achieved before pregnancy, compared to an increase of 33% when seizure control was established prior to pregnancy. A similar disparity was observed in cases of focal epilepsy with different localizations; however, the percentage of seizure exacerbation was significantly lower (26% and 5%, respectively).

In an observational cohort study conducted in Nigeria, a higher likelihood of seizures during pregnancy was observed in cases of structural focal epilepsy with posttraumatic (p=0.013) and infectious etiology (p=0.041). The authors also noted that the absence of seizures for less than 6 months before pregnancy had an unfavorable impact on pregnancy outcomes (p=0,043) [2].

The review by M.J. Eadie [9] is dedicated to analyzing the dynamics of seizures during pregnancy over the past 50 years. There was a trend towards the worsening of seizure control. Factors contributing to this worsening included: the use of AEDs with lower teratogenic potential, non-compliance, the pro-epileptic influence of female sex hormones, a more unfavorable course of FE compared to IGE, seizure remission before conception for less than 9–12 months, and the use of polytherapy (likely indicating pharmacoresistant disease). Additionally, negative influences on the course of epilepsy during pregnancy include: non-compliance with sleep-wake cycles (especially in IGE); pregnancy-related vomiting; anxiety and depression [4].

As shown in Table 1, almost all publications over the past 10 years note a trend towards an increase in seizures during pregnancy [9].

In a limited number of studies dedicated to the dynamics of the disease during pregnancy in the absence of AED therapy, seizures also increased [14].

Our experience indicates the impossibility of predicting the influence of a previous pregnancy on the course of the current one [4].

In summary, achieving seizure control for 9 months before pregnancy significantly increases the likelihood of its maintaining during pregnancy [5]; the likelihood of seizure absence during pregnancy is 59.5% for FE, 73.6% for IGE, and on average – 66.6% [7]; frontal FE most frequently exacerbates during pregnancy compared to FE of other localizations [8], and the likelihood of increased seizures during pregnancy is higher for structural FE (trauma/encephalitis) [2]; status epilepticus during pregnancy is observed in 0.55% of cases [7]. Maintaining a stable health condition during pregnancy significantly depends on compliance, avoiding smoking and alcohol, sufficient night sleep (especially in IGE), and timely treatment of anxiety/depression [4].

Epileptic Seizures: Risk for Mother and Fetus

The main objective of using AED is to prevent seizure occurrence during pregnancy, as they have unfavorable effects on both the mother and the fetus/child. Generalized tonic-clonic seizures (GTCS) and focal seizures transitioning to bilateral tonic-clonic seizures (BTCS) have the most detrimental impact on the mother (risk of traumatic brain injury, limb injuries, spinal injuries, blunt abdominal trauma, hypoxia, lactic acidosis [4], sudden unexpected death in epilepsy (SUDEP) [15], etc.) and the fetus (asphyxia, hypoxia, trauma [1], distress syndrome [16], potential reduction in size and weight of the newborn, and premature birth [17]). All other types of seizures, if not associated with the pregnant woman falling, have minimal impact [4].

Currently, there is no proven link between seizures and the occurrence of congenital malformations (CM) in the fetus [1], although there are prerequisites for their occurrence in prolonged GTCS, BTCS, or GTCS status due to severe hypoxia and acidosis. Depending on the stage of pregnancy at which the seizure occurs, a miscarriage may happen. At the same time, prospective studies have not proven the impact of GTCS on the development of the nervous system [18, 19].

Pharmacokinetics of AEDs During Pregnancy

During pregnancy, starting from early stages, significant changes in the pharmacokinetics of AEDs are observed, including changes in absorption, increase in volume of distribution, enhancement of renal excretion, and induction of hepatic metabolism. Summary data on predicting AED concentrations during pregnancy with an unchanged daily dose are presented in Table 2.

As indicated in Table 2, the most unstable pharmacokinetics during pregnancy are observed with the use of PB, PHT, OXC, LTG, TPM, LEV, ZNS, up to a critical reduction to 65% of the pre-pregnancy level [10, 20, 21]. A decrease in concentration by just 35% can lead to an increase in epileptic seizures.

Impact of AEDs on Fetal Growth and Development

The impact of mono- or polytherapy with AEDs on fetal growth and physical development has been studied based on several national registries and population studies (Australia, Denmark, EURAP, Finland, NAAPR, NEAD, Norway, Russia [22], Sweden, UK and Ireland Epilepsy and Pregnancy Registers). The findings suggest a possible intrauterine growth retardation of varying severity when the mother uses polytherapy during pregnancy, as well as monotherapy with AEDs such as primidone, PHT, CBZ, VPA, TPM, ZNS, with TPM having the most negative impact among the new AEDs [1].

Teratogenesis

Currently, AEDs with minimal (LTG and LEV), moderate (PB, TPM), and maximal (VPA) teratogenic potential have been identified (Table 3) [1]. However, according to a nationwide cohort study conducted in France (n = 1,886,825), no significant associations with CM were found for LTG, LEV, OXC, and CBZ [23]. For drugs with high and moderate risks of congenital malformations, a direct correlation between the frequency of CM and the increase in daily dose, primarily for VPA, has been shown [1].

Table 1. *Dynamics of epileptic seizures during pregnancy (according to [9], with addition)*

Author	Number of pregnant women (n)	Number of women (n)	Seizure reduction rate (%)	Seizure exacerbation rate (%)
Battino D. et al., 2013 [7]	3806	3451	12%	15,8%
Reisinger T.L. et al., 2013 [10]	115	95	17,4%	38,3%
Cagnetti C. et al., 2014 [11]		272	17,5%	23,4%
La Neve A. et al., 2015 [12]	56		8%	19%
Shahla M. et al., 2018 [13]		94	25,5%	28,7%
Pennell P.B. et al., 2020 [6]		351	14%	23%
Voinescu P.E. et al., 2022 [8]	114	99	–	FE – 21,1%; IGE – 5,3%

Impact of AEDs on Child Development and Behavior

In "cognitive teratogenesis," as in structural/anatomical teratogenesis, VPA holds the "first place", as it is associated with a dose-dependent risk of cognitive impairments, nervous system development disorders, autism spectrum disorders, attention deficit hyperactivity disorder (ADHD) [28], developmental problems in infancy [29], reduced IQ and cognitive functions in childhood [30] and school age [31]. Even small

doses of VPA (<400 mg/day) were associated with reduced verbal IQ and increased need for educational assistance [18, 19, 32].

According to studies, CBZ does not cause serious neurobehavioral disorders [19, 33, 34]. Children born to mothers who received PHT showed better IQ results than those exposed to VPA and comparable results with children of mothers in the CBZ and LTG monotherapy groups [19, 32]. In another study, children whose mothers received LTG during pregnancy had IQs comparable to those in the control group [19], and in terms of early development and school performance, LTG showed better results compared to children whose mothers received VPA [18].

For LEV, TPM, and other AEDs, information on their impact on cognitive abilities and behavior in later childhood is limited [1]. It should be noted that the absence of evidence of harm should not be perceived as a proof of the safety of a particular AED. When preparing for pregnancy, patients should be informed about current data on the risks and benefits of individual AEDs.

Table 2. *Summary data on the prediction of concentration of anticonvulsants during pregnancy at a constant daily dose (according to [1], with modifications)*

AED	Decrease in serum concentration	Decrease in serum free (unbound) concentration	Recommendations to perform therapeutic drug monitoring, if available
Phenobarbital (PHB)	Up to 55%	Up to 50%	Yes
Phenytoin (PHT)	60–70%	20–40%	Yes, free concentration
Carbamazepine (CBZ)	0–12%	None	Optional
Valproate (VPA)	Up to 23%	None	Optional, free concentration
Oxcarbazepine (OXC) monohydroxy – derivative (MHD)	36–62%	not applicable	Yes
Lamotrigine (LTG)	0.77 of population: 69% decrease 0.23 of population: 17% decrease	not applicable	Yes
Topiramate (TPM)	Up to 30%	not applicable	Yes
Levetiracetam (LEV)	40–60%, with maximal decrease reached in the first trimester	not applicable	Yes
Zonisamide (ZNS)	Up to 35%; data is limited	not applicable	Yes

Managing Pregnancy in Epilepsy

Drug therapy. According to the latest recommendations from the working group on providing care to women during pregnancy, no significant associations have been found between the use of LTG, LEV, OXC, and, to a lesser extent, CBZ during pregnancy and the occurrence of congenital malformations in the fetus [1]. It is considered axiomatic to avoid the use of VPA and PHT in women of childbearing age [35]. If discontinuation of VPA is not possible, therapy should be conducted with two AEDs at the minimum dose of VPA, using LTG, LEV, OXC, or CBZ as the additional drug.

Folic Acid Supplementation. Several studies have shown that the addition of folates reduces the number of congenital heart defects [36], decreases the incidence of autism spectrum disorders [37], and increases IQ [18] in children born to mothers with epilepsy who took AEDs. However, there are also risks associated with high doses of folic acid: increased risk of cancer, cognitive disorders, and cleft palate [38].

Recommendations for the daily dose of folic acid vary significantly, ranging from 0.4 mg/day [20] to 5 mg/day [1]. The high risk of unplanned pregnancies necessitates that women of childbearing age take folates at a dose of at least 0.4 mg/day. Doses above 0.4 mg/day are recommended if there are malformations in the family history. In our practice, we recommend regular intake of 3 mg of folic acid 1–2 months before conception and during the first 12 weeks of pregnancy [39].

Preparation for Pregnancy. The primary task of the neurologist and epileptologist is to achieve medical remission of epilepsy for at least 9 months before the planned pregnancy using monotherapy at the minimum dose of AEDs. Practice shows that a seizure-free period of 6 months is often sufficient, but further data accumulation on this issue is needed [4]. The necessity of continuous AED intake is justified by the rule that "a generalized convulsive seizure is more dangerous for the

Table 3. *Prevalence of major congenital malformations on monotherapy, according to four prospective registries (according to [1], with amendment)*

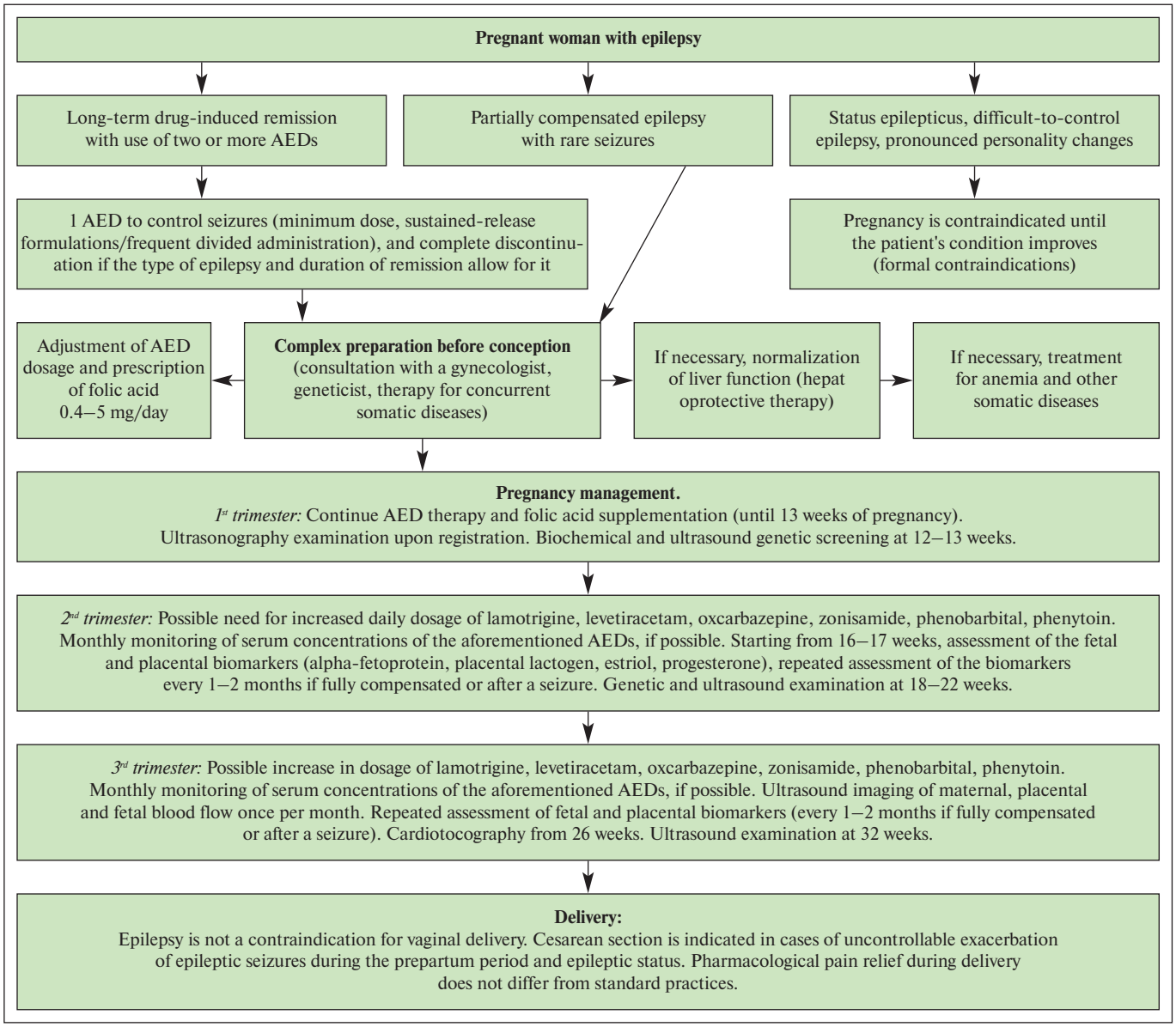
AEDs	Prevalence of major congenital malformations, %			
	EURAP [24]	NAAPR [25]	UK and Ireland [26]	Australia [27]
CBZ	5.5	3.0	2.6	5.5
VPA	10.3	9.3	6.7	13.8
PNB	6.5	5.5	–	–
TPM	3.9	4.2	4.3	2.4
LTD	2.9	2.0	2.3	4.6
LEV	2.8	2.4	0.7	2.4
PNT	6.4	2.9	3.7	–
OXC	3.0	2.2	–	–

patient and her child than continuous AED intake" [1, 4, 22, 39]. Additionally, it is essential to exclude somatic pathology, primarily anemia, and to determine the functional state of the liver and kidneys, which are involved in the metabolism and excretion of AEDs.

The algorithm for preparing for pregnancy and managing pregnancy is presented in the figure.

During pregnancy, starting from the end of the first trimester, due to increased renal blood flow, there may be a decrease in the concentration of LEV, LTG, OXC, ZNS, PHT, benzonal, and PHT. The concentration of LTG in the blood can decrease up to three times. Therefore, the physician should know the baseline level of these AEDs in the blood before pregnancy and strive to maintain this level. Experts from the International League Against Epilepsy (ILAE) recommend monitoring the concentration of these AEDs every 4 weeks. A clinically significant decrease in concentration is a reduction in blood levels by one-third. In this situation, the daily dose of AEDs is increased by 30–50%. If it is not possible to measure the concentration of AEDs during pregnancy, it is recommended to increase the daily dose by 30–50% at the end of the first trimester for patients who were on the minimum dose of AEDs, had GTCS (and other seizures that could lead to falls), or were taking AEDs with variable pharmacokinetics (LTG, LEV, OXC, ZNS, PHT, PHT). The issue of increasing the daily dose should also be considered in cases of short, unstable remission, in patients with significant structural brain changes, and when conducting polytherapy that includes AEDs with variable pharmacokinetics [1].

Assisted Reproductive Technologies. During in vitro fertilization (IVF) with the use of high doses of estrogens, there is a risk of seizure recurrence due to the pro-epileptic effect of estrogens, as well as a decrease in LTG concentration in the blood by two times or more. In cases of long-term, stable clinical remission,



Algorithm for pregnancy planning, pregnancy management and delivery in patients with epilepsy [40]

the recommendations are to continue regular AED intake and adhere to a sleep-wake schedule. If the primary disease is not sufficiently compensated, it is advisable to measure the baseline AED level in the blood and during the administration of sex hormones before the ovarian stimulation procedure [39]. If the AED concentration decreases by one-third, it is recommended to increase the daily dose by 30–50%. If it is not possible to determine the LTG concentration, the AED dose should be increased by 50% before IVF.

Managing Pregnancy. Formal contraindications to pregnancy include: difficult-to-treat epilepsy with frequent seizures accompanied by falls, GTCS, or focal seizures transitioning to BTCS; status epilepticus; and severe personality changes that pose a threat to the health and life of both the mother and the fetus [4, 39]. These are considered formal because if a woman decides to become pregnant, neurologists and obstetricians are obligated to use all available means to maintain the pregnancy.

Given the certain risk of congenital malformations (CM), a consultation with a geneticist is mandatory. Invasive genetic testing methods are conducted as indicated.

For compensated epilepsy with seizure remission, the regularity of visiting a neurologist is once every 2 months, and obstetrician-gynecologist visits are according to standard guidelines. For observed focal seizures, neurologist visits should be once a month, and obstetrician-gynecologist visits should be once every 2–3 weeks. It is strongly recommended that patients and their relatives contact an epileptologist if there is any increase in seizure frequency.

The determination of AED concentrations is conducted once every 2 months or less frequently for compensated epilepsy, and once a month or at each visit for observed seizures. In practice, during the first trimester of pregnancy, it is essential to measure the concentrations of AEDs with variable pharmacokinetics: LTG, LEV, OXC, PB, TPM, ZNS, as increased renal blood flow at the end of the first trimester can increase clearance and reduce their concentrations. For LTG, not only renal blood flow but also changes in pharmacokinetics play a role: increased glucuronidation and conjugation of the drug can cumulatively reduce LTG concentration by three times [41, 42].

Status Epilepticus. GTCS status and focal seizures transitioning to BTCS are treated according to the 2022 recommendations [43, 44]. Along with generally accepted obstetric indications, status epilepticus and uncontrolled increase in seizure frequency in the pre-delivery period justify performing a cesarean section [39]. Status of focal seizures without and with altered consciousness, and status of absences are not indications for pregnancy termination or cesarean section. Cesarean section is performed in all cases based on obstetric indications, except for status GTCS and BTCS in the pre-delivery period.

Delivery, Pain Management, and Pregnancy Outcomes. Epilepsy is not a contraindication for vaginal delivery. The medical management of labor and pain relief in epilepsy does not differ from usual practices.

In the vast majority of cases, women who underwent preconception preparation experienced favorable pregnancy and epilepsy outcomes: 78% of women were in remission throughout the pregnancy; 20% carried the pregnancy without AEDs, and 80% received monotherapy with minimally effective doses of AEDs. Pregnancy complications observed included the threat of miscarriage, anemia, toxicosis, and preeclampsia, which were mostly mild and regressed with treatment. The frequency of congenital malformations and minor anomalies in newborns did not exceed the general population rate [4].

Postpartum Management. Due to the risk of epilepsy exacerbation in the postpartum period, it is strongly recommended to maintain regular AED intake and adhere to a rest regimen [1, 4].

The reduced need for AEDs after childbirth can lead to the possibility of overdose due to the relative increase in drug concentration caused by weight loss, blood loss during delivery, changes in AED absorption, and other factors. In the postpartum period, it is advisable to return to the daily dose used before pregnancy (if the daily dose of AEDs was increased during pregnancy). The normalization of LTG pharmacokinetics occurs within 3 weeks postpartum [1]. In practice, we have not observed signs of AED overdose in the postpartum period [39].

Seizure Risks and Child Safety Any epileptic seizures with altered consciousness and seizures with a risk of falling, such as GTCS, focal seizures transitioning to BTCS, atonic, myoclonic, and myoclonic-tonic-clonic seizures, pose a danger to the child. If seizures persist or there is a threat of their occurrence/recurrence, it is recommended that a relative stays with the mother to assist in child care [39]. Breastfeeding should be done in a lying position. Refusal to breastfeed the newborn is entirely unjustified, as the exposure to AEDs in the child's blood during pregnancy is usually higher than through the mother's milk [1].

Vitamin K Administration. Currently, there is insufficient data to confirm or refute the necessity of administering vitamin K to the newborn in the early postpartum period when the mother is taking AEDs that stimulate the cytochrome P450 system [20]. In our practice, we did not additionally prescribe vitamin K, as previous studies indicate a balanced hemostasis system in newborns regardless of the AED used [45].

Conclusion

The issue of "Epilepsy and Pregnancy" is continuously being studied, but much remains to be explored. The difficulties in analyzing publications lie in the small sample sizes, insufficient quality of conducted studies, and the ethical impossibility of conducting double-blind placebo-controlled studies. Therefore, the main recommendations for managing "epilepsy during pregnancy" / "pregnancy in epilepsy" are based on expert opinions rather than evidence. However, steady progress in this area is evident, especially in recent years. A significant achievement is the publication of "Management of epilepsy in pregnancy: a report from the International League Against Epilepsy Task Force on Women and Pregnancy" [1, 46], which addresses the main issues, directions for further research, and recommendations for preparing and managing pregnancy in patients with epilepsy. In 2020, the same group of researchers conducted a global survey of national ILAE chapters. It was found that many countries use outdated or overly general guidelines on the issue, while information is significantly updated annually. A series of ILAE pages on Wikipedia containing recommendations for pregnancy in women with epilepsy is planned [47].

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