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# Managing epilepsy in women of childbearing age — Polish Society of Epileptology and Polish Gynecological Society Guidelines

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## THE PURPOSE AND SCOPE OF THE GUIDELINES

Epilepsy is the most common neurological disorder during pregnancy [1]. About one-third of women with epilepsy are of childbearing age. Statistically, between 0.3% and 0.5% of births occur in women with epilepsy [2]. Every year in Poland epilepsy poses a threat to the health of some 1800 pregnant women and their fetuses. According to British studies, the risk of death in pregnant women with epilepsy increases tenfold compared to pregnant women without epilepsy, mainly due to sudden unexpected death in epilepsy (SUDEP) [3]. Diagnostic and therapeutic advances in the field of epilepsy have contributed to better seizure control. As a result, more and more women with epilepsy become pregnant and more than 90% give birth to healthy children [4, 5]. In order to avoid irregularities in the management of women suffering from epilepsy, it is very important to create standards for the management of women treated for epilepsy, both for those who are already pregnant and those who plan pregnancy. Thus the first edition of guidelines regarding management and care in women with epilepsy during preconception period and also during pregnancy, delivery, and postpartum were prepared by the experts of Polish Society of Epileptology and Polish Gynecological Society. The diagnosis, seizures classification and therapy of epilepsy were not included into the guidelines.

The neurologists, gynecologists and family doctors should inform that the women with epilepsy could benefit from planning pregnancies to reduce the risk of fetal congenital malformations. Due to increased awareness and knowledge concerning epilepsy, the number of planned pregnancies is increasing, but 40% are still unplanned. The risk of major congenital malformations in the fetus increases in women with epilepsy taking antiepileptic drugs [6]. Fears of women with epilepsy in relation to the adverse effects of antiepileptic drugs on infants can lead to arbitrary withdrawal or dose reduction of antiepileptic drugs, and thus increase the risk of seizures and even SUDEP [4]. Therefore, women of reproductive age (15–44 years) treated for epilepsy should receive care from specialist epilepsy and gynecology clinics.

## DIAGNOSIS OF EPILEPSY

Epilepsy is a heterogeneous group of diseases of the brain, the common symptoms of which are clinical seizures. After diagnosis of epilepsy, a neurologist determines the type of epileptic seizure and suggests appropriate treatment for epilepsy. Based on the course of the disease, neurologist can assess the degree of risk of neurological complications in pregnancy. Women who have not experienced seizures for at least 10 years (including five years without antiepileptic drugs) and those who were diagnosed with childhood epileptic syndrome, but have not experienced seizures in

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their adult life are considered as no longer suffering from epilepsy [7]. Women with a history of epilepsy who have no risk of unprovoked epileptic seizures may be classified as a low-risk group. Uncontrolled tonic-clonic seizures are the strongest risk factors for SUDEP, which is the main cause of death in pregnancy [3]. Seizures occurring for the first time in the second half of pregnancy do not have to be of epileptic origin and eclampsia treatment should be implemented according to the agreed protocol until a final diagnosis is reached. Tonic-clonic seizures in eclampsia combined with loss of consciousness are often preceded by an increase in blood pressure, proteinuria, thrombocytopenia and an increase in serum transaminase. However, in nearly 40% of cases, these irregularities may only appear within 24 hours [8]. A differential diagnosis should also take account of other causes, such as cardiac, metabolic, or psychogenic reasons [8]. Psychogenic non-epileptic seizures can coexist with epileptic seizures and are a complex diagnostic and therapeutic problem requiring multidisciplinary psychological and psychiatric management.

## PRECONCEPTION CARE IN WOMEN WITH EPILEPSY

The purpose of preconception care in women with epilepsy is to reduce the risk of fetal abnormalities and disorders of the subsequent development of the child through the optimization of pharmacological treatment and folate supplementation, as well as to control seizures in pregnancy. It is important to explain the problem to the patient and her relatives and emphasize that the potential teratogenic factor, i.e. an antiepileptic drug, starts working in the first days after conception. At least until the end of the first trimester of pregnancy, the lowest effective dose of the most appropriate AED should be used in order to reduce the risk of major birth defects [6]. Withdrawal of medication for at least a year before the planned pregnancy can be considered in women after a three-year seizure-free period [9]. Pregnant women who have experienced seizures a year before conception require increased monitoring and treatment for epilepsy. Most women (67%) do not experience seizures during pregnancy. Between 74% and 92% of women who have been seizure-free for at least 9 months to 1 year before pregnancy will remain free of seizures during pregnancy [4]. Data from EURAP (European Registry of Antiepileptic Drugs and Pregnancy) have shown that pregnant women with idiopathic generalized epilepsy are more likely to be free of seizures (74%) than those with focal epilepsy (60%) [10]. Women with epilepsy should be informed that a few safety precautions can greatly reduce the risk of seizures and minimize concern about the impact of AEDs on their infants. Studies have shown that 87% of women would like to consult their doctors on the impact of seizures and antiepileptic drugs on their unborn children, and about half of them would like to be more active in the discussion about their treatment [11]. Moreover, if risk factors for the inheritance of epilepsy are known or if a patient feels very strong anxiety and fear that her child will inherit the disease, she should be offered genetic counseling.

### Antiepileptic drugs and their teratogenic effects

Women with epilepsy who plan to become pregnant should be under the care of physicians with expertise in the treatment of epilepsy. The women should consciously participate in the choice of drugs and doses on the basis of reliable information about the related risk to the fetus and the control of seizures in the mother. Women with epilepsy should be informed about the fact that the majority of women give birth to healthy children, and the risk of congenital defects is low if the child is not exposed to AEDs during the periconceptional period. In women with epilepsy not using AEDs, the risk of congenital defects in children is similar to that in the population [6].

The risk of major birth defects of the fetus is dependent on the type, nuber and dose of AEDs Among AEDs, lamotrigine (LTG), levetiracetam (LEV), carbamazepine (CBZ) and oxcarbazeine (OXC) used in monotherapy in small doses cause the least risk of major malformations in the offspring [6, 10, 12–14]. The most common major birth defects associated with AEDs involve the neural tube, heart, urinary tract, skeletal system and cleft palate. Sodium valproate causes an increased risk of neural tube defects, facial cleft, hypospadias; phenobarbital (PB) and phenytoin (DPH) may cause heart defects; DPH, CBZ, topiramat (TPM) may lead to cleft palate in the fetus. It is worth noting that PB and DPH are used extremely rarely in the Polish population. A systematic review and meta-analysis of 59 studies estimating the incidence of congenital malformations in the fetuses of mothers using different AEDs indicate that the highest risk of congenital malformations in fetuses occurs in women taking sodium valproate (10.7 of 100, 95% CI: 8.16–13.29) or combination therapy (16.8 of 100, 95% CI: 0.51–33.05) compared to the fetuses of mothers not suffering from epilepsy (2.3 of 100, 95% CI: 1.46–3.1) [13]. The EURAP's data show that the lowest rates of malformations were observed in women who received LTG in a dose less than 300 mg per day (2 of 100, 95% CI: 1.19–3.24) and CBZ in a dose less than 400 mg per day (3.4 of 100, 95% CI: 1.11–7.71) [10]. The rates of major congenital anomalies in the records of Great Britain and Ireland were also lower in women taking levetiracetam (LEV) in monotherapy (0.7 of 100, 95% CI: 0.19–2.51) than in the group that took combination therapy (5.6 of 100, 95% CI: 3.54–8.56) [14]. There are insufficient data, including the small amount of pregnant women, to assess the risk of birth defects for other AEDs used in monotherapy,

such as gabapentin (GBP), lacosamide (LCM), oxcarbazepine (OXC), pregabalin (PGB), topiramate (TPM) and zonisamide (ZNS) [6]. However, although available data on the use of new-generation AEDs are still limited, they indicate that these drugs have a favorable safety profile and cause a lower risk of teratogenic effects than the older drugs. The risk of major birth defects in a subsequent pregnancy is increased (16.8 of 100) if it occurred in a child in a previous pregnancy.

There were no significant relationships between the type of epilepsy, tonic-clonic seizure in the first trimester of pregnancy and birth defects. Women with epilepsy and their partners should be informed about the possible adverse effects of sodium valproate on the long-term neural development of the fetus in the womb [6]. Studies of preschool children whose mothers took valproate during pregnancy show that as many as 30–40% of these children experience delays in the early stages of development such as delays in talking and walking, poorer intellectual abilities, poor language skills (speaking and understanding), memory impairment and autism spectrum disorders. Compared to mothers without epilepsy and mothers with epilepsy not receiving AEDs, the intelligence quotient (IQ) measured in school-age children (6 years) exposed to valproate in utero was an average of 7–10 points lower than in children exposed to other antiepileptic drugs (data indicate that the risk of deterioration of intellectual abilities may be independent of the mother's IQ) [15, 16]. Based on limited evidence, CBZ and LTG do not seem to have this effect. In 2014, the Cochrane Review demonstrated that there are no significant differences in the development and IQ of children exposed to antiepileptic drugs, such as CBZ, LTG and DPH, compared with the infants of mothers without epilepsy and the offspring of women with epilepsy not taking AEDs [17]. Very few studies have so far evaluated the cognitive abilities of the children of mothers using LEV during pregnancy, but preliminary results involving a limited number of respondents suggest a slight risk of teratogenicity. Parents should be informed that data concerning the long-term sequelae of AEDs are based on observations of a small number of children. Little is known about other new AEDs and the use of combination therapy, but the lack of data should not be interpreted. Literature data and messages for healthcare professionals should be monitored on a regular basis, as they may contain new information on this subject.

### Folate supplementation

Antiepileptic drugs are a risk factor for reduced blood folate levels. Folate metabolism disorder is associated with a higher incidence of fetal abnormalities, such as neural tube defects, miscarriage, preeclampsia and intrauterine fetal growth inhibition [18]. When used in the periconceptional period, folates may have a beneficial effect on reducing the risk of deficits associated with exposure to AEDs [19]. Folate supplementation should begin at least three months before pregnancy and be continued during pregnancy, the postpartum period and breast-feeding.

The recommended dose in women taking antiepileptic drugs is 400 µg plus another 400 µg, preferably in the form of active folate [20]. High doses of folate, 5 mg daily, are recommended only if the woman or her partner and their offspring suffer from neural tube defects. The use of doses above 5 mg is not justified and could lead to a lowered seizure threshold.

## ANTENATAL CARE

Pregnant women with epilepsy should have access to regular, planned antenatal care provided by an interdisciplinary team, preferably in specialist centers ensuring the highest level of perinatal and neurological care. Women taking antiepileptic drugs who have become unintentionally pregnant should have an urgent opportunity to discuss the procedure with a specialist to avoid a sudden reduction or withdrawal of AEDs without proper consultation. From the moment of conception, pregnant women should consult a gynecologist-obstetrician at least every four weeks and a neurologist at least once a trimester.

### Maternity care during pregnancy

Physicians providing care for pregnant women with epilepsy should be aware of a small but significant increase in the risk of complications during pregnancy, especially in women taking AEDs [4, 5, 21]. A review of 38 studies of women with epilepsy conducted in 2015 showed that there was a slightly higher risk of: spontaneous abortion (OR 1.54, 95% CI: 1.02–2.32); antepartum hemorrhage (OR 1.49, 95% CI: 1.01–2.20); hypertensive disorders (OR 1.37, 95% CI: 1.21–1.55); induction of labor (OR 1.67, 95% CI: 1.31–2.11); cesarean section (OR 1.40, 95% CI: 1.23–1.58); premature birth (less than 37 weeks; OR 1.16, 95% CI: 1.01–1.34); fetal growth inhibition (OR 1.26, 95% CI: 1.20–1.33); and postpartum hemorrhage (OR 1.29, 95% CI: 1.13–1.49) in women with epilepsy compared to women without epilepsy [5]. No differences were found between the two groups in terms of perinatal death. A comparison of women with epilepsy taking and not taking AEDs showed a higher risk of induction of labor (OR 1.40, 95% CI: 1.05–1.85), fetal growth inhibition (OR 3.51, 95% CI: 1.23–10.01) and postpartum hemorrhage (OR 1.33, 95% CI: 1.16–1.54) in the group receiving AEDs. There were no significant differences between the two groups in terms of hypertensive disorders, cesarean section, spontaneous abortion, antenatal hemorrhage, preterm birth and fetal death. Studies comparing women receiving monotherapy and polypharmacy showed a greater risk of cesarean section in the group receiving combination therapy (OR 1.47,

95% CI: 1.07–2.02). There were no differences in spontaneous miscarriage, premature birth (before 36 or 37 weeks) and antepartum hemorrhage in both groups. There were also no differences in gestational age and stillbirths.

Due to an increased risk of fetal abnormalities, pregnant women with epilepsy should have ultrasound scans (which are generally recommended in pregnancy) performed by qualified professionals. Ultrasound performed in the first and second trimesters of pregnancy can detect abnormalities in the anatomy of the fetus. If fetal defects are detected, perinatologists and neonatologists must consult in order to identify therapeutic opportunities during and after pregnancy. Parents should be able to choose the procedure.

The children of women with epilepsy taking AEDs have an increased risk of lower weight in relation to gestational age. A physician performing an ultrasound examination in the third trimester of pregnancy should pay special attention to fetal biometry. Fetal health should be monitored in pregnancies with fetal growth restriction. It is recommended to perform fetal biometry and ambulatory cardiotocography after 36 weeks in pregnancies not complicated by fetal growth restriction.

Antiepileptic drugs, such as phenytoin, carbamazepine and phenobarbital may increase the metabolism of corticosteroids, which in turn can lead to reduced therapeutic efficacy for the prevention of respiratory distress syndrome in infants in women with epilepsy taking enzyme-inducing AEDs, who are at risk of premature birth. However the benefits of increase dose of corticosteroids have not been proved and, the routine doubling of corticosteroid dose is not recommended [22].

### Neurological care during pregnancy

Risk factors for seizures, such as lack of sleep, stress, irregular intake of AEDs, as well as the type and frequency of seizures should be evaluated in pregnant women with epilepsy. If women who are at a high risk of seizures have to be admitted to hospital before labor has begun, they should be placed in a location that allows the medical personnel or relatives to continuously monitor the patients. During subsequent visits to the clinic, mothers should always be examined for their ability to cope with daily duties, memory, concentration, sleep quality, dose regimen, as well as the frequency and type of seizures. Symptoms such as an increase in the number of seizures, fatigue, dizziness, as well as the occurrence of potential risk factors for seizures such as lack of sleep and stress may require consultation with a neurologist, who may change the dose of medication, add new drugs or recommend hospitalization. Women with frequent seizures are advised to stay with a companion for as long as possible. Patients with seizures that occur during sleep or without witnesses are at a high risk of SUDEP [3]. It is recommended that these patients are not left unattended at night.

Serum concentrations of most of new generation antiepileptic drugs may fluctuate during pregnancy due to changes in pharmacokinetics at the stages of absorption, metabolism, excretion and hemodilution. It has been found that concentrations of lamotrigine, levetiracetam and oxcarbamazepine in pregnant women may fall by as much as 30% to 50% [6]. Reduced concentrations of drugs can exacerbate seizures. Some doctors prophylactically increase the dose of drug during pregnancy, while others have concerns about the potential side effects of increased intake of drugs during pregnancy without clear preponderance of benefit over risk. It is therefore recommended to monitor the concentration of these drugs in blood serum before pregnancy and at least once in each trimester of pregnancy. It is recommended that women with epilepsy are informed that some types of epilepsy and some AEDs carry an increased risk of depression, depressed mood, poor concentration, fatigue, irritability or anger [11]. It is emphasized that women should be encouraged to perform self-observation.

## DELIVERY IN WOMEN WITH EPILEPSY

Perinatal care of pregnant women with epilepsy should take place in specialist centers providing the highest level of perinatal and neurological care. Women with epilepsy should be reassured that the majority will have uncomplicated deliveries and receive appropriate care in the event of complications.

The diagnosis of epilepsy per se is not an indication for planned cesarean section or induction of labor. There is no indication for earlier delivery in women with epilepsy without obstetric risk factors whose seizures are well controlled. Cesarean section may be considered for a small percentage of women with a significant increase in seizures, cluster seizures and a high risk of status epilepticus. Obstetrical procedures in women with epilepsy do not deviate from accepted principles of modern obstetrics. However, continuous cardiotocographic monitoring is recommended during labor.

Pregnant women with epilepsy should be informed that the risk of seizures during labor is low and ranges from about 1% to 2% and from 1% to 2% within 24 hours after birth. Antiepileptic drugs should be continued during labor according to neurologist's recommendations. If they cannot be administered orally, they should be administered parenterally (valproic acid, levetiracetam and phenytoin are administered intravenously). Seizures during labor can lead to hypoxia in the mother (due to apnea during seizure), as well as fetal hypoxia and acidosis secondary to increased tension of the uterus. Adequate hydration and pain relief by epidural anesthesia reduces the risk of seizures during labor. Nitrous oxide can also be used as an analgesic. Administration of pethidine

is contraindicated because of the risk of a lowered seizure threshold. Early use of epidural anesthesia can minimize risk factors for seizures during labor, such as: hyperventilation, sleep deprivation, pain and stress. If general anesthesia is required, anesthetics such as pethidine and ketamine must be avoided (they decrease the seizure threshold).

There are no known contraindications to the use of any labor-inducers in women with epilepsy taking AEDs. There is no evidence that antiepileptic drugs affect labor-inducing medications. It must be noted that risk factors, such as stress, insomnia and dehydration increase in women with prolonged induction and efforts should be taken to minimize them.

## THE POSTPARTUM PERIOD IN WOMEN WITH EPILEPSY

Due to increased stress, lack of sleep, anxiety and missing a dose, the immediate period after birth involves a high risk of more frequent seizures. Mothers should be supported in the postpartum period to minimize risk factors for seizures; in particular, they should be provided with a continuous 4–6 hour period of sleep [19]. Taking AEDs is not a contraindication to breastfeeding, because the benefits outweigh the risks. Many women receive higher doses of antiepileptic drugs in late pregnancy compared with the doses used before pregnancy. In the postpartum period, the physiological changes that take place during pregnancy, such as increased renal and liver clearance and hemodilution, are reversed and there is a risk that high doses of AEDs will be toxic for the newborn. If the dose is increased during pregnancy, the concentration of the drug should be measured within 10 days after delivery and the dose should be adequately reduced in order to avoid toxicity after delivery [6, 19]. If signs of toxicity of AEDs are observed in the postpartum period (e.g. drowsiness, double vision or balance disorder), urgent neurological evaluation is required.

Neonates born to women taking AEDs should be monitored for adverse effects (drowsiness, difficulty in breastfeeding, excessive sedation or withdrawal symptoms — excessive irritability and crying) associated with exposure to AEDs in utero. Care for women with epilepsy and their children should be provided by perinatological centers having the ability to determine concentrations of AEDs and cooperating with neurological centers specializing in care for patients with epilepsy.

Women with epilepsy who take antiepileptic drugs during pregnancy should be encouraged to breastfeed. Mothers should be informed that according to current knowledge, the risk of cognitive complications is not increased in children exposed to antiepileptic drugs contained in the milk of mothers taking AEDs [6, 19]. It must be remembered that all antiepileptic drugs penetrate into the mammary gland and are secreted in breast milk. However, their concentration is much lower in the milk than in the serum of a breastfeeding patient. A lack of breastfeeding may cause abstinence syndrome in the newborn, which is more dangerous than breastfeeding. The symptoms of drowsiness in the newborn may occur in cases where the mother is administered high doses of phenobarbital, primidone and benzodiazepines. In such cases, cessation of breastfeeding should be taken into account. A prospective study has shown that the psychomotor development of children who were exposed to antiepileptic drugs in utero and breastfed in the postpartum period was better after 6 and 18 months compared with children who were not breastfed or were breastfed for less than 6 months [6, 19]. Women who had no seizures during pregnancy can breastfeed their babies. However, those who experienced seizures should breastfeed only in the presence of a family member or medical personnel, if possible.

Women with epilepsy are at an increased risk of depression in the postpartum period compared with mothers without epilepsy. Symptoms of postpartum depression include depressed mood, fatigue, lack of appetite, and feelings of tension or anxiety. Early intervention can improve the quality of women's lives.

## CONTRACEPTION IN WOMEN WITH EPILEPSY

Contraception is a key problem for women with epilepsy of childbearing age. Planning and conscious preparation for pregnancy allows women to choose the least burdensome drug (with the lowest risk of teratogenicity), start increased supplementation of folic acid, as well as to optimize seizure control in the periconceptional period [23]. Contraceptive methods in patients with epilepsy should be selected according to criteria used for the entire population, taking into account additional criteria: the impact of contraceptives on the severity of the disease; the impact of contraceptives on the effectiveness of antiepileptic drugs; the impact of antiepileptic drugs on the effectiveness of contraceptives. Previous studies have shown no impact of non-hormonal contraceptives on any of the above criteria [24].

### Hormonal contraception

Regardless of the form and route of administration, combined contraception increases the incidence of seizures through the three main mechanisms [24, 25]: 1) direct, non-genomic effect on neuronal receptors (GABA and other receptors); 2) direct genomic effect on intracellular targets such as steroid receptors; 3) indirect effect on the metabolism of antiepileptic drugs through the induction of cytochrome P450 enzymes. Antiepileptic drugs can induce the cytochrome P450 family of hepatic enzymes and isoenzyme 3A4 in particular by increasing the metabolism of ethinyl estradiol (EE), and consequently decrease the effectiveness of birth control [26].

The American Academy of Neurology recommends the use of oral contraceptives containing 50 micrograms of EE. While this is an expert opinion, there are no studies proving that pills containing 50 micrograms of EE in combination with the anti-inducers of liver enzymes are more effective. There are currently no preparations of similar composition on the Polish market because of their proven harm! Transdermal patches and vaginal rings have the same sensitivity to selected antiepileptic drugs.

Gestagen-only contraceptives are less sensitive to liver enzyme inducers and are the recommended method of hormonal contraception in women with epilepsy [27]. Continuous methods are particularly recommended, such as the levonorgestrel intrauterine device and subcutaneous etonogestrel implant. However, in the case of intramuscular administration of medroxyprogesterone acetate, shortening the time between injections, to 8–10 weeks instead of the standard 12 weeks, is suggested. Not all antiepileptic preparations have enzyme-inducing effects. Table 1 lists the drugs that reduce the effectiveness of contraception and those that have no effect on it [28]. Special attention should be paid to lamotrigine. The use of oral contraceptives reduces its concentration by nearly 50% [29]. In contrast to other antiepileptic drugs, lamotrigine is eliminated by binding to glucuronic acid [30]. Patients receiving hormonal contraception in combination with lamotrigine should have its serum concentration monitored due to a possible reduction in the effectiveness of antiepileptic treatment. Published studies have shown no effect of progestin-only contraceptives on lamotrigine concentration [23].

**Table 1. Antiepileptic drugs and their impact on the effectiveness of hormonal contraception**

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| **Antiepileptic drugs that reduce the effectiveness of contraception** |
| Carbamazepine |
| Felbamate |
| Lamotrigine — only reduces the level of progesterone |
| Oxcarbazepine |
| Phenobarbital |
| Phenytoin |
| Primidone |
| Rufinamide |
| Topiramate — reduces the level of ethinyl estradiol by about 30% |
| **Antiepileptic drugs that do not affect the effectiveness of contraception** |
| Acetazolamide |
| Benzodiazepines: clobazam, clonazepam |
| Ethosuccimide |
| Gabapentin |
| Lacosamide |
| Levetiracetam |
| Pregabalin |
| Sodium valproate |
| Tiagabine |
| Vigabatrin |
| Zonisamide |

**Table 2. Contraception in women with epilepsy**

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| Barrier methods of birth control and the intrauterine device with copper may be recommended according to the rules applicable in the whole population |
| Gestagen-only contraceptives, which are less sensitive to liver enzyme inducers, are the recommended method of hormonal contraception in women with epilepsy<br>The levonorgestrel intrauterine device and subcutaneous etonogestrel implant are the contraceptive methods whose effectiveness are not affected by antiepileptic drugs inducing P450 enzymes and should be recommended as first-choice contraceptives<br>In the case of intramuscular administration of medroxyprogesterone acetate, the time between injections must be shortened to 8–10 weeks |
| Regardless of the form and route of administration, combined estrogen-progestogen contraceptives increase the incidence of seizures and should not be used in women with epilepsy |

**Managing Epilepsy in Women of Childbearing Age — key points**

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| Epilepsy is not a contraindication to having children: more than 90% of women with epilepsy give birth to healthy children |
| The planning and preparation for pregnancy are essential and necessary in women with epilepsy |
| The fetal malformations' risk stratification should reflect the type and dose of AEDs, and the use of mono or polytherapy regiments |
| Epilepsy is not a contraindication to natural vaginal birth, epidural childbirth and breastfeeding |
| Effective contraception is possible in women with epilepsy who do not plan pregnancy |

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