REVIEW / DERLEME

How Should Antiepileptic Drugs Be Selected During Pregnancy

Gebelikte Antiepileptik Seçimi Nasıl Olmalı?

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Summary

Although the risk of prematurity, growth retardation, and major malformations is higher in infants of mothers using antiepileptic medications than in those of the mothers not using them, the harmful effects of the convulsive seizures on the maternal and fetal health are much more. Thus, the risks introduced by the antiepileptic medications to the fetus as well as the effects of the seizures occurring during gestation on maternal and fetal health should be evaluated carefully. Both antiepileptic medications and seizures may negatively impact the fetus. Given that recently introduced antiepileptic medications have fewer side effects they are used widely and due to their high tolerability rates, several investigations regarding their efficacy have been prompted in pregnant women. On the contrary, the teratogenic effects of the old-generation antiepileptics and their negative effects on cognition warrant more careful use of these medications. The primary objective in choosing antiepileptic medications for pregnant women is to control the seizures and minimize the risk of developing both physical and cognitive malformations.

Keywords: Antiepileptic treatment; cognitive malformation; epilepsy; gestation; teratogenicity.

Özet

Antiepileptik ilaç kullanan annelerin bebeklerinde prematüre, gelişme geriliği ve major malformasyon riski; ilaç almayanlara göre daha yüksek oranda olmasına rağmen, konvülsif nöbetlerin anne ve bebek sağlığına olan zararlı etkileri çok daha fazladır. Bu yüzden antiepileptik ilaçların fetüse getirdiği riskler ile gebelik sırasında oluşan nöbetlerin anne ve bebek sağlığına etkisi dikkatlice değerlendirilmelidir. Hem antiepileptik ilaçlar, hem de nöbetler fetüsü olumsuz yönde etkileyebilir. Son zamanlarda yeni çıkan antiepileptik ilaçların yan etkilerinin az olması ve toleransın yüksek olması özelliklerinden dolayı yaygın kullanılmaya başlanmış olması, bu ilaçların gebelerde olan etkinliğinin araştırılmasına neden olmuştur. Bununla birlikte eski kuşak antiepileptiklerin bilinen teratojenik etkileri yanında kognisyon üzerine etkilerinin olumsuz olması da bu ilaçların daha dikkatli kullanılmasını gerektirmektedir. Gebelikte antiepileptik seçiminde birincil amaç; nöbetleri kontrol altına almak, bebeğin hem fiziksel hem de kognitif malformasyon gelişme riskini en aza indirmektir.

Anahtar sözcükler: Antiepileptik tedavi; kognitif malformasyon; epilepsi; gebelik; teratojenite.

Introduction

Epilepsy is one of the most common neurological diseases. Studies have reported its prevalence to be 0.5%. Most epileptic patients women are at reproductive age. Despite the fact that epileptic women can give birth to healthy children, premature birth, low birth weight, risk of fetal and neonatal death, congenital malformations, and growth retardation rates are higher in epileptic women than in normal populations. Seizures, antiepileptic drugs (AEDs), and genetic and socioeconomic reasons can affect fetal health negatively.

The teratogenic effects of AEDs are one of the most important criteria determining clinician's selection of an ap-

propriate AED during this period. Several studies showed an increase in teratogenic side effects in mothers using AEDs. The incidence of major and minor congenital malformations in children of epileptic mothers is approximately twice of that in the general population.[1,2] Congenital malformations seen in infants of epileptic pregnant women are divided into two categories: major and minor. Malformations that may lead to death or severe functional loss are referred to as major congenital malformations.[3] Major congenital malformations occur during organogenesis, which is the first 3–8 weeks of pregnancy.[4] The most commonly encountered major congenital malformations are cardiac defects, urogenital malformations, craniofacial defects, and skeletal anomalies similar to those seen in the general population.[5] Although the prevalence of these malformations is 1.6%–3.2% in the community, it is 2.3%–7.8% in pregnant women using AED monotherapy and 6.5%–16.8% in pregnant women receiving polytherapy.[3] The minor congenital malformation is a congenital malformation that can reduce or prevent the loss of function that may occur during extremity and organ development which does not lead to death or serious functional loss even if not treated.[6] The most common minor variations in children of epileptic mothers are dysmorphic face, low birth weight, hyper-

telorism, hypoplasia of the nail and distal phalanges, and decreased height and head circumference.[6] These are seen 2–2.5 times (6%–20%) more frequently than in the normal population.[2]

Cognitive Malformations

Besides major and minor congenital malformations, another important issue addressed in recent studies was the negative effects on cognitive functions. For example, the incidence of mental retardation in the normal population is 1%, but it is 1.6%–6% in children of epileptic pregnant women.[7] It has been shown that negative cognitive impairment occurs in the children of women who give birth after using AEDs such as valproate, phenobarbital, diphenylhydantoin and topiramate. It has been suggested that these malformations are caused due to the effect of AEDs on fetal maturation[8] (Table 1).

A recent study showed that lower intelligence quotient, and verbal and memory abilities were detected in children of mothers using valproate than in those using carbamazepine, lamotrigine, and phenytoin. Moreover, the negative effect of valproate on cognition increases with higher doses.[9] The use of phenobarbital in the last trimester has

Table 1. Studies on antiepileptic drug–dependent cognitive response

Study	Results
Gilham et al. 1991	Decision making and reaction times were worse in the polytherapy group than in the monotherapy and control groups.
McKee et al. 1992	Valproate has no significant effects on decision making, taking action, and verbal learning.
Donati et al. 2007	No significant evidence on cognitive impairment and data processing time while comparing sodium valproate, CBX, and OXC was obtained.
Prevey et al. 1996	No difference in cognitive impairment caused by carbamazepine and VPA was observed. No effects on motor speed, memory, concentration, mental absence, and coordination were reported.
Craig-Tallis et al.1994	Sodium valproate and PB caused a minor reduction in cognitive function.
Spitz et al. 1991	No cognitive side effects were detected.
Stores et al. 1992	A small difference was detected between antiepileptics. Better performance was observed when the patients needed attention.
Meador et al. 2003	Cognitive problems caused by sodium valproate: memory (17%), speech (7%), attention (10%), psychomotor slowing (3%), confusion.
De Araujo Filhou et al. 2006	Sodium valproate had a better effect on the attention components than TPM, such as verbal fluency and short-term memory.
Glauser et al. 2010	More attention problems were observed with sodium valproate than with ESM and LTG.
Bromley R 2014	Low IQ levels were detected with sodium valproate exposure during pregnancy. The effect of new antiepileptic drugs is unknown.

Source: (Clare M. Eddy, Hugh E. Rickards, Andrea E. Cavanna. The cognitive impact of antiepileptic drug. Ther Adv Neurol. Disord (2011) 4(6) 385-407.)

CBZ: Carbamazepine; ESM: Ethosuximide; LTG: Lamotrigine; OXC: Oxcarbazepine; PB: Phenobarbital; VPA: Na valproate; TPM: Topiramate.

a negative impact on cognitive skills such as attention and memory. When phenytoin is used at high doses, mental impairment becomes more pronounced. Contradictory results have been reported for carbamazepine. No harmful effects of carbamazepine on cognition were observed when compared with oxcarbazepine and valproate. Topiramate has significant negative effects on cognition. In particular, it has negative effects on attention, memory, and language functions. Although number of studies are limited, no negative effects of levetiracetam (LEV) on cognition were detected previously. The effect of lamotrigine on memory is unclear. Available evidence shows that it increases awareness. Vigabatrin has no negative or positive effect on cognition. Insufficient studies are available on gabapentin, tiagabine, zonisamide, and rufinamide.[10] Studies showing the effects of AEDs on cognition are summarized in Table 1.

Epileptic Seizures During Pregnancy

Epileptic seizures increase during pregnancy in approximately one third of the cases.[2] Some studies have reported an increased risk both for the infant and the mother during the first trimester.[11,12] Some other studies have shown an increase of risk during the last trimester as well.[13–15]

In the International Registry of Antiepileptic Drugs and Pregnancy (EURAP) study, the probability of having a postpartum seizure was 3%. According to this study, the incidence of seizures during or after childbirth was low in the cases who had not had any seizures until birth.[16]

The first reason of increased seizures is the treatment uncompliance. Patients either stop medication or reduce the doses in order to avoid the side effects of antiepileptic treatment. Another reason is the physiological changes in pregnancy. The total body fluid increases in pregnancy, and the volume in which of drug dissolves increases which results in decreased drug levels. Liver cytochrome P450 enzymes are induced and renal clearance increases. As a result of these alterations, drug blood levels are reduced. In pregnancy, albumin level decreases, albumin-bound drug level decreases, and free drug level increases. All of these physiological changes can lead to increased seizures. Third, psychiatric problems are frequently observed in pregnancy. Anxiety disorders, depression, and sleep deprivation may facilitate the emergence of epileptic seizures.[17,18] Also, estrogens and progesterone, which have important roles during pregnancy, might lead to increased number of epileptic seizures.

[19,20] In general, estrogen reduces whereas progesterone increases seizure threshold.[21,22]

Studies conducted in human and animal models have shown that estrogen increases the excitability of the central nervous system and has some epileptogenic properties which might lower the seizure threshold, whereas progesterone has features that increase seizure threshold. Estrogen shows some epileptogenic aspects by suppressing the neurotransmission of gamma-amino butyric acid (inhibitory effect) and enhance the neurotransmission of glutamate (excitatory effect). Progesterone has opposite effects in the central nervous system.[23]

Use of Antiepileptic Drugs During Pregnancy

A large research community investigating the effects of antiepileptic use on pregnancy and infant and epileptic seizures, called the EURAP, has been working with 42 countries since 1999.

The primary objective in choosing antiepileptic medications for pregnant women is to control seizures with the least administered AED doses. The best tolerable drug with the least risk of side effects and teratogenicity should be administered at the lowest dose to provide seizure control.[24]

Demographics, comorbidities, family characteristics, genetic inheritance, drug treatments, and types of seizures were reviewed in the study of the EURAP group. Patients were categorized according to their seizure frequency (no seizures, daily seizures, once a week, more than once a week, or more than once per month). The generalized tonic–clonic seizure was investigated as a secondary seizure or a status seizure. Seizure statuses have been determined to be convulsive or nonconvulsive. It was emphasized that 23% of the seizures may be nonconvulsive, 58.3% of the seizures are generalized tonic–clonic or secondary generalized seizures, and 18% of the seizures were a combination of tonic–clonic and nonconvulsive seizures. It was reported that 220 pregnancies had premature births in 1956.

Pregnant women use AEDs as mono- or polytherapy at different ratios. These are carbamazepine (CBZ), lamotrigine (LTG), oxcarbazepine (OXC), phenobarbital (PB), diphenylhydantoin (PHT), and valproic acid (VPA). The rate of monotherapy treatment was found to be 78.7%, whereas the rate of polytherapy treatment was found to be 21.3%.

No treatment change was required in 62.7% of the cases. Drug changes were made in only 12 of pregnant women. The number of medications was reduced for 57 pregnant women and increased for 51 pregnant women. The drug dose was increased approximately for one fourth of the pregnant women in the second and third trimesters.

The use of polytherapy is an independent risk factor in increasing seizure frequency. Similarly, an increase in seizure type may occur associated with the localization.

Even if the drug group is small, OXC has been reported to be risky for convulsive seizures. Larger-sample studies are needed to provide precise information on this.

Despite a marked improvement in 15.9% of the cases in the second and third trimesters, 17.3% of the cases experience more frequent seizures in second and third trimesters.

In this study, convulsive seizures were encountered in 36 patients (1.8%) which was more prevaelent during the third trimester. Only one patient was reported to have a nonconvulsive seizure during labor.[16]

This study has aimed to discuss the risks of congenital malformations associated with the most frequently used AEDs and their probable effects on cognition in the context of recently published studies.

A. First-Generation Antiepileptic Drugs
Valproic Acid

VPA is an effective drug in many types of generalized and partial epileptic seizures.[25] Several studies have been performed regarding its use in pregnancy. A class II study showed that VPA increased the risk of MCMs in epileptic pregnant women receiving VPA either as mono- or polytherapy.[26] Another class I study found the risk of MCMs to be higher in patients receiving VPA polytherapy than in those receiving any polytherapy without VPA. A class I study investigating the absolute risk of major congenital malformation (MCM) revealed the risk to be 2.2% for carbamazepine, 6.2% for valproate, 3.2% for lamotrigine, and 3.7% for phenytoin.[27] The highest dose causing MCM has not been confirmed yet, but it was found to be approximately 1000 mg/day in five studies.[28–30]

Additionally, as mentioned earlier, the teratogenic effects of VPA on cognitive abilities have also been shown to be dose-related.[9]

Carbamazepine

CBZ is used for treating simple and complex partial epileptic seizures and generalized convulsions. Different results have been obtained in different studies on the cause of congenital malformations. A class I study has shown that children of epileptic women using CBZ do not have an increased risk of MCMs.[27] Another study reported an increase in the occurrence of orofacial cleft due to in- utero exposure to CBZ compared with the control group.[31]

Thomas and colleagues have shown that the risk of cardiac malformations after CBZ monotherapy was 6.3%.[32]

Phenytoin

PHT is one of the most commonly used drugs for both generalized and partial seizures as an antiepileptic. Phenytoin teratogenesis has been studied by researchers for nearly 40 years. The risk of MCMs has been shown to increase by two- to threefold in pregnant women using PHT than in pregnant women not using it.[33] Many studies have shown a linear relationship between exposure to in utero PHT and the risk of developing MCMs.[34–36]

In terms of cognitive teratogenicity, phenytoin adversely affects mental speed when used in high doses in polytherapy.[10]

Phenobarbital

Since PB is an antiepileptic drug with sedative and hypnotic properties that induce hepatic metabolism, doses of co-administered drugs should be adjusted carefully. The risk of MCMs with monotherapy in epileptic pregnant women was 4.9% in one study.[35] The most common malformations with phenobarbital are distal phalanx hypoplasia, epicanthus, short nose, low ear, lip anomalies, hypertelorism, and cardiac defects.

B. Second-Generation Antiepileptic Drugs
Lamotrigine

LTG is one of the newer-generation antiepileptics with broad-spectrum effects. It has been frequently used in recent years. The malformation rate with lamotrigine was reported as 2.9%. No specific malformation type has been

reported. According to the international LTG data, 12 MCMs were reported in 414 pregnant women receiving LTG monotherapy in the first 3 months. This was similar to the incidence of MCMs in the general population. Perhaps the most important thing to keep in mind about LTG is the increased risk of malformations when combined with valproate.[37]

In 2006, Morrow et al. found the risk of MCMs to be lower in 647 pregnant women receiving LTG than in those receiving VPA. The risk of MCMs for LTG was 3.2%; it was 3.5% for the control group not using any drug and 6.2% in the children of pregnant women receiving VPA.

Many studies reported that neural tube defects were less frequent in epileptic pregnant women using LTG than in those using VPA.[38]

In animals, dosage studies with LTG showed its toxic effects at a dose of 20 mg/(kg/day), leading to 20% weight loss in mothers and low birth weight in the baby. Doses of 5–10 and 15 mg/(kg/day) had no such effects.[39]

In 2008, Holmes et al. found an increase in the risk of orofacial cleft occurrence compared with the control group as mono- and polytherapy in pregnant women receiving LTG. [40] A study conducted by Hunt et al. (1151) reported an isolated cleft palate in only one of the pregnant women that was receiving LTG as monotherapy.[41]

Another remarkable aspect of LTG is that it might increase the risk of a seizure due to decreased plasma levels during the second and/or third trimester.[42–47]

Therefore, the teratogenicity of LTG is still unclear; however, the limited amount of data has demonstrated that LTG is less teratogenic than VPA and phenytoin.[48] At the same time, evidence shows that lamotrigine increases attention on cognition.[10] It is noteworthy that the rate of LTG use in pregnant women is increasing day by day.

Topiramate

TPM is used in patients with partial and primary generalized epilepsy.[49] Only two studies have reported on TPM use in pregnancy and shown that exposure to TPM during pregnancy leads to increased in birth defects. The first one was conducted by Hunt et al. in 2008; they found the rate of MCMs as 4.8% in the children of 70 pregnant women re-

ceiving TPM during pregnancy. The rate of MCM with TPM polytherapy was 11.2%, which was approximately threefold higher than the rates when TPM was used as monotherapy [50] Another study was conducted by Holmes et al. in 2008, which showed that the risk of developing congenital malformations in 197 pregnant women using TPM was 4.1%.[51] According to the report of the North American Antiepileptic Drug and Pregnancy Commission, the risk of MCMs was reported as 3.8% in pregnant women receiving topiramate in the first trimester (n=289); this rate was 1.3% in the group not receiving the drug. Low birth weight was found in infants exposed to TPM (9.8%), and this ratio was 3.6% in the controls.[52]

Since palate and lip clefts have been observed in the babies of women using TPM during pregnancy in recent years, the Food and Drug Administration (FDA) changed the pregnancy category of TPM from C to D in 2011. Also, its negative effect on cognition was clearly defined.[10]

Levetiracetam

LEV is increasingly used by women of childbearing age, and the general impression is that they are better tolerated and have fewer side effects. However, the teratogenic effects of LEV are unknown.[53]

Holmes et al. (1979) found, using data from the North American Epilepsy Registry, the risk of MCMs to be 2.3% during the analysis of 197 pregnancies in the largest study of pregnant women who received LEV monotherapy in the first trimester.[51]

Other Antiepileptic Drugs

Some malformations related to gabapentin, pregabalin, tiagabin, zonisamide, lacosamide, and oxcarbazepine monotherapies have also been reported. However enough information has not yet been obtained regarding rates. Animal studies on the use of lacosamide in pregnancy have shown an increase in embryo/fetal mortality, perinatal mortality, and developmental deficit. The pregnancy category was determined as C by the FDA. No controlled study has been performed in humans. Only drugs with high benefit/risk ratio can be tried.[54]

One of the most comprehensive studies on second-generation antiepileptic drugs evaluated 6653 patients who received TPM in the EURAP trial; the major malformation rate

Table 2. Antiepileptic drugs, risks of congenital malformations, and suggestions

AED	FDA pregnancy	Related risks	Suggestions about their use in pregnancy
CBZ	C	Cardiac malformations	Low teratogenic potential compared with PB and VPA
GBP	C	No related major congenital malformation in monotherapy	Limited data showed lower teratogenic risk compared with classical AEDs
LTG	C	No clear major congenital malformation pattern	Limited data showed lower teratogenic risk compared with classical AEDs
LEV	C	Pyloric stenosis (with lamotrigine in phototherapy), spina bifida (CBZ and VPA in polytherapy)	Limited data showed lower teratogenic risk compared with classical AEDs
OXC	C	Urogenital malformation	Limited data showed lower teratogenic risk compared with classical AEDs
PB	D	Cardiac malformation	Should be avoided in women at reproductive age
PHT	D	Bradycardia and hypotension, fetal hydantoin syndrome	Should be avoided in women at reproductive age
TPM	C	Hypospadias, hare-lip	Limited data showed lower teratogenic risk compared with classical AEDs
VPA	D	Cardiac malformations, hypospadias, low lip anomaly, neural tube defect, porencephaly, spina bifida	Should be avoided in women at reproductive age

AED: Antiepileptic drug; CBZ: Carbamazepine; GBP: Gabapentin; LTG: Lamotrigine; LEV: Levetiracetam; OXC: Oxcarbazepine; PB: Phenobarbital; PHT: Phenytoin; TPM: Topiramate; VPA: Valproic acid (Nitin K. Sethi, Amy Wasterlain. Pregnancy and epilepsy: when you are managing both. The Journal of Family Practice, Vol 59, No. 12, December 2012).

was found to be 0.6%, and the incidence of syndrome was 0.2%. Malformation was not observed in 93.4% of the cases. [55] The risks and recommendations related to old- and new-generation antiepileptic drugs, FDA pregnancy category, and gestational use are summarized in Table 2.

Factors Affecting AED Choice during Pregnancy

All female epileptic patients at reproductive age should be informed about the teratogenic potential of AEDs, importance of folic acid use, possibility of discontinuing or changing antiepileptic drugs, expected frequency changes during pregnancy, importance of compliance to treatment, and the necessity of AED blood level follow-up before pregnancy.[56,57]

As drugs are selected, the lowest dose in accordance with the patient's seizure type, which provides the control of monotherapy and seizures, should be preferred in divided doses. Since all of the classical antiepileptics have a high teratogenic index, they should not be selected as the first choice in a woman who plans to become pregnant. If this treatment has been started previously, dose adjustments should be made at least 6 months before gestation. Classical AEDs used (carbamazepine, phenobarbital, phenytoin, primidone valproate) are class D drugs in terms of fetal effects. Although they are known to have teratogenic effects on the fetus, they can be used during pregnancy (Table 2).

It should kept in mind that the risk of teratogenicity increases with the dose increments and the number of drugs used in polytherapy. Therefore, polytherapy should be avoided as much as possible. In particular, polytherapy containing valproate should be avoided. Valproate inhibits the metabolism of other antiepileptic drugs and increases the formation of teratogenic metabolite intermediates.

The suggestions in terms of AED discontinuation for patients who plan pregnancy and other patients are similar. These patients should be followed more frequently. Drug discontinuation should not be considered in juvenile myoclonic epilepsy, symptomatic epilepsies, and idiopathic generalized epilepsy with electroencephalographic impairment.[56,57]

Patients should start to take folic acid 1–3 months before pregnancy and continue to take it for at least the first 3 months of gestation. The recommended dose for all women at reproductive age is 0.4–0.6 mg/day. Patients who have a history of neural tube defect in their families, or those taking sodium valproate or carbamazepine, should take 4–5 mg folic acid daily. It has been noted that preconceptional use of 4 mg folic acid reduces neural tube defect formation by 50%.[58] In women using enzyme-inducing AEDs (CBZ, PHT, PRM, PB), 20 mg/day prophylactic vitamin K should be given in the last month of pregnancy for protection against neonatal hemorrhagic disease, associated with the lack of clotting factors. 1 mg of parenteral vitamin K should also be given to the baby.[59] AED level follow-ups should be performed monthly at the beginning of each trimester and at the end of trimester of pregnancy. Moreover, if seizure control is not successful, the control frequency can be increased.[56]

Challenges That Physicians Faced during Daily Practice
Many challenges exist during the follow-up of epileptic pregnant women, these patients are frequently directed to third-step health centers.

Many factors contribute to the development of malformations such as genetic predispositions, harmful effects of drug metabolism, interaction of drugs with folate metabolism, when it is a folate antagonist, depression of cardiorespiratory functions, drug binding to fetal tissue, and hypoxia due to maternal seizures.[60] The reasons to explain the increase in epileptic seizures during pregnancy include hormonal (increase in serum estrogen), metabolic (increase in sodium and water retention), psychological (increase in stress and anxiety), physiological (increase in sleep deprivation), and pharmacokinetic mechanisms.[61] A study confirmed that all four antiepileptic drugs (CBZ, PHT, VPA, and PB) were associated with congenital malformations. Nonetheless, CBZ appeared to be the safest drug among these four antiepileptic drugs.[61]

Lamotrigine is the most recommended AED in epileptic patients, especially for pregnant women. The majority of patients under the lamotrigine treatment are seizure-free.[60]

The most common problem is that patients admit to hospital after pregnancy. Alterations in drug treatment regimen should be done at least 6 months before getting pregnant. However, if the patient comes for control late and if her sei-

zures are under control with monotherapy, the AED should not be changed. It is necessary to add folic acid at the dose of 4–5 mg/day.

Some patients discontinue their medications during pregnancy due to expected harmful effects on the baby, and therefore their seizure frequency increases. The underlying causes of increased frequency of epileptic seizures during pregnancy in the first trimester are vomiting, insomnia, excessive daytime sleepiness, irregular dosing of medications, changes in the pharmacokinetics of certain drugs in pregnancy, and social problems.

The three points that need the attention of physicians are seizure control, treatment alterations (number of medications and doses), and congenital malformations. All three issues must be followed closely.[62]

If the patient's polytherapy and seizures are under control, a transition to monotherapy is only possible with a close follow-up of the patient.

If possible, the use of sodium valproate should be avoided in treating epilepsy during pregnancy, and if it is absolutely necessary, it should be kept under the dose of 800–1000 mg/day. Sodium valproate should not be included in the polytherapy protocols.

The level of blood alpha-fetoprotein (AFP) in the 16th week of pregnancy is helpful to avoid 75%–80% of the neural tube defects (NTDs). Also, the ultrasonography in the 18th–19th weeks makes 94% of the diagnoses. The probability of developing NTDs in pregnant women with normal AFP level and ultrasonographic findings is less than 1%.[63,64]

The incidence of seizures increases in one third of epileptic pregnancies during pregnancy. Recent studies found the rate of occurrence among all the pregnancies to be 6 in 1000 and the incidence of convulsive status to be 3 in 1000.[62]

Normal vaginal delivery might be a safe option for epileptic women. However, 1%–2% of women have seizures during labor. It should not be forgotten that nonconvulsive seizures may be also seem like convulsive seizures during delivery. In case of seizures, short-acting benzodiazepines should be used. It should not be forgotten that the baby

may be sedated severely and have respiratory distress. Patients should continue to take their medicines during labor. Epidural anesthesia may also be preferred.[63] However, cesarean delivery should be preferred in the case of a treatment-resistant seizure or if the seizure frequency increases during the last period of the pregnancy. Hyperventilation should be avoided during labor.[65]

All of the major antiepileptic agents pass through the milk in small doses. Epilepsy itself or AED use is not a contraindication to breastfeeding. Women receiving phenobarbital, primidone, and benzodiazepine during postnatal breastfeeding period should be warned about possible sedation effects of these drugs on the baby. Although no clear opinion exists about the optimum time, the plasma levels of the drugs should also be controlled. In case of sedative side effects, nutritional difficulties and irritability and lactation might be discontinued.[66–68]

Conclusions

Recently, the effects of epilepsy and the use of antiepileptic drugs on fertility, pregnancy, teratogenicity, and physical and cognitive development of newborn have gained interest. In addition to the mechanism of action and side effects of antiepileptics, it is also important to know their appropriate indications and doses in special circumstances including pregnancy. An epileptic pregnant woman using antiepileptic drugs should be referred to an obstetrics and gynecology specialist. The treatment of women at reproductive age who are planning a pregnancy is important both for the mother and the baby. Pregnancy can affect the seizures of the patients. The number of seizures increases in about three quarters of pregnant women. Moreover, the effects of pharmacodynamics and pharmacokinetic of antiepileptic drugs can change during pregnancy. However, the most important problem is the teratogenic effects of antiepileptic drugs. The treatment of epileptic pregnant women is one of the most important challenges in epilepsy.

The use of new antiepileptic drugs such as LEV and LTG in the first trimester appears to be safer. However, since the number of pregnant patients using these new AEDs is limited, it would not be appropriate to comment on this drug.

Regarding all these reasons, epileptic women should be followed by specialists (neurology and obstetrics and gynecology) before, after, and during pregnancy. This study aimed to review problems frequently encountered in epileptic pregnant women.

Conflict of interest
None declared.

Authorship contributions
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