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Review

Antiepileptic drugs and Pregnancy: A brief review

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ABSTRACT

Epilepsy affects approximately 1 percent of the population and roughly 1 million women of childbearing age. Estimates suggest that 0.3-0.7 percent of pregnancies occur in women with epilepsy. Epilepsy itself increases the risk of congenital malformation and medications add to this risk. Also, approximately one-half of the use of medications for epilepsy are used for other indications, possibly increasing exposure in some women. As controlled trials with these medications are not performed during pregnancy, data has been accumulated primarily through databases and case studies. This review is intended to update the practitioner about the use and concerns of antiepileptic medications in the pregnant woman and the potential effects on the fetus and neonate. We searched PubMed database for articles published from January 2020 to May 2024. We used 'Pregnancy' and 'Antiepileptic drugs' keywords. Of the total articles screened (n = 1153), seventeen publications were finally included in this review.

Keywords: epilepsy, pregnancy, antiepileptic drugs, congentital malformation

INTRODUCTION

Convulsions are dangerous to women with epilepsy not only because of the risk of seizure-related falls and blunt trauma but also because of potential harm to the fetus from the possibility of hypoxemia and asphyxia. Focal seizures that do not evolve to convulsions are thought unlikely to have a major impact on the fetus, but anecdotal evidence indicates that they may cause transient fetal distress, with fetal heart rate deceleration for up to 2.5 minutes. The fundamental reason that women with epilepsy are continuously treated with antiepileptic drugs throughout pregnancy is to avoid the recurrence of seizure activity and its related adverse effects.[1] All practitioners who care for women with epilepsy should be familiar with the relevant information and provide counseling when an antiepileptic drug is first prescribed and yearly on how epilepsy and its treatment may interact with their contraception, conception, and pregnancy. Counseling should be tailored to each patient, depending on their age,

seizure burden, and antiseizure medication exposure. This article provides brief information to guide practitioners in the management of epilepsy in pregnancy.

Valproate in Pregnancy

One study identified all pregnancies exposed to valproate in the Kerala Registry of Epilepsy and Pregnancy between January 2010 and December 2019. Subjects' past usage of antiepileptic drugs, seizure count before and during pregnancy, fetal outcome, and major congenital malformations were abstracted from the registry records. The presumed reason for the usage of valproate was deducted from the clinical records. There were 221 pregnancies (17.75%) exposed to valproate (monotherapy, *n* = 149) during the audit period. The major congenital malformations rate for the completed pregnancies exposed to valproate was higher (*n* = 20, 10.36%) than that of valproate unexposed pregnancies (*n* = 39, 4.96%). The relative risk for major congenital malformations with valproate exposure was 2.1 (95% confidence interval = 1.24–3.48, the number needed to treat with valproate to result in major congenital malformations = 19). Reasons for using valproate during pregnancy (some women had more than one reason) were (1) valproate was the first antiepileptic drug prescribed and was effective (68, 29.06%), (2) other antiepileptic drugs were ineffective (128, 54.70%), and (3) other antiepileptic drugs were discontinued due to adverse effects (17, 7.28%). Other reasons (21, 8.97%) were (1) valproate was selected after the epilepsy classification was revised (3, 1.28%), (2) other antiepileptic drugs were expensive (2,.85%), and (3) patients switched to Valproate from other antiepileptic drugs for an unspecified reason (16, 6.83%). Valproate was discontinued during pregnancy for 6 (2.71%) persons. Less than 10% of women were tried on lamotrigine or levetiracetam before switching to Valproate.[2]

Levetiracetam in Pregnancy

Levetiracetam is increasingly used in pregnant women with epilepsy. Although teratogenic effects have not been observed so far, data on the risks of spontaneous abortion and major birth defects are still limited, especially for the frequently used dual therapy of levetiracetam and lamotrigine. One study aimed to analyze rates of major birth defects and spontaneous abortion after maternal levetiracetam treatment. Based on pregnancies recorded by the Embryotox Center from 2000 to 2017. Outcomes of prospectively ascertained pregnancies with first-trimester levetiracetam monotherapy (*n* = 221) were compared to pregnancies with lamotrigine monotherapy for epilepsy (*n* = 469). In addition, all pregnancies with levetiracetam (*n* = 364) exposure during the first trimester were analyzed in comparison to a nonexposed cohort (*n* = 729). Pregnancies with the most frequently used combination therapy comprising levetiracetam and lamotrigine (*n* = 80) were evaluated separately. The study confirms the use of levetiracetam as a suitable antiepileptic drug in pregnancy. The lower birth weight of male neonates after maternal levetiracetam monotherapy and the unexpectedly high risk of spontaneous abortion and birth defects after dual therapy with levetiracetam and lamotrigine require further investigation.[3]

Valproate, Gender, and autism spectrum disorder

Prenatal exposure to the antiepileptic drug valproic acid is associated with an increased risk of impaired postnatal neurodevelopment, including autism spectrum disorder and attention-deficit hyperactivity disorder. One study aimed to evaluate the influence of gender and drug dosage on the association between prenatal valproate exposure and postnatal behavioral outcomes. The Australian Pregnancy Register of antiepileptic drugs was interrogated to identify children aged 4-11 years prenatally exposed to antiepileptic drugs. Parents reported their child's behavior using the Autism Spectrum Quotient–Children's Version and the National Institute for Children's Health Quality Vanderbilt Assessment Scale

for attention-deficit hyperactivity disorder. General linear mixed-effects models were used to investigate the relationship between clinicodemographic variables and psychometric scores. 121 children were studied: 54 were prenatally exposed to valproate (28 males, 26 females; mean dose ± SD: 644 ± 310 mg/day), and 67 were exposed to other antiepileptic drugs. There was a main effect of gender showing higher autism spectrum disorder scores in males compared to females (p = .006). An interaction between gender and valproate exposure revealed that males had higher autism spectrum disorder symptoms among children exposed to antiepileptic drugs other than valproate (p = .01); however, this typical gender dynamic was not evident in valproate-exposed children. There was no evidence of any dose-response relationship between valproate exposure and autism spectrum disorder symptoms. Males had higher attention-deficit hyperactivity disorder scores compared to females, but there was no evidence of a link between attention-deficit hyperactivity disorder symptoms and valproate exposure.[4]

Therapeutic Drug Monitoring of Antiepileptic Drugs

During pregnancy, the pharmacokinetics of an antiepileptic drug are altered because of changes in the clearance capacity and volume of distribution. These changes may have consequences for the frequency of seizures during pregnancy and fetal exposure to antiepileptic drugs. During pregnancy, an increase in clearance and a decrease in the concentrations of lamotrigine, levetiracetam, oxcarbazepine's active metabolite licarbazepine, topiramate, and zonisamide were observed. Carbamazepine clearance remains unchanged during pregnancy. There was inadequate or no evidence for changes in the clearance or concentrations of clobazam and its active metabolite N-desmethyl clobazam, gabapentin, lacosamide, perampanel, and valproate. If the antiepileptic drug concentration changes more than 25% compared with the reference concentration, dose adjustment is advised.[5]

Major congenital malformation risk

A large multinational population-based study and a large meta-analysis, suggest that the major congenital malformation rate is 2%-3% in women without epilepsy and about 3% in women with epilepsy who were unexposed to antiepileptic drugs during pregnancy. Data from the meta-analysis also suggest that the major congenital malformation rate is approximately population level at 2.6%-3.5% with levetiracetam and lamotrigine and that it is about 4%-5% with carbamazepine, 2.8%-4.8% with oxcarbazepine, about 4% with topiramate, about 5%-7% with phenytoin, about 6%-9% with phenobarbital, and nearly 10% with valproate. The major congenital malformation risk with valproate is significantly higher than that with other antiepileptic drugs (including topiramate and phenobarbital) which significantly increases the risk.[6]

Antiepileptic drugs and attention deficit hyperactivity disorder

One study reviewed evidence on the risk of attention deficit hyperactivity disorder after maternal exposure to new-generation antiepileptic drugs during pregnancy. Lamotrigine monotherapy holds the largest body of evidence, concluding that no significant risk of attention deficit hyperactivity disorder exists among the offspring. However, the available evidence is considered scarce and has several methodological limitations. Disentangling the effect of antiepileptic drugs from epilepsy itself and examining polytherapy are challenges that merit additional investigations. Further comparative safety studies with longer follow-up periods and large sample sizes are needed to accurately quantify the true impact of new-generation antiepileptic drug exposure during pregnancy and attention deficit hyperactivity disorder in children.[7]

Interaction of Antiseizure Medication and Oral Contraceptives

Oral hormonal contraceptives are almost exclusively absorbed through the intestines, and many of them are metabolized to an inactive compound by the cytochrome P450 P3A4 (CYP3A4) enzyme. Antiseizure medications that are CYP3A4 enzyme inducers accelerate the hepatic metabolism of both the estrogenic and progestogenic components of systemic hormonal contraceptives. They decrease the duration and intensity of contraceptives' efficacy by reducing their circulating levels and causing potential contraceptive failure. This occurs with phenytoin, phenobarbital, and carbamazepine, potent CYP3A4 inducers. Antiseizure medications that do not induce CYP3A, such as lamotrigine, levetiracetam, and zonisamide (TABLE 2-2), are not expected to affect hormonal contraceptives with a significant impact.[8]

Gestational Hypertension and Preeclampsia

A pooled analysis including 17 studies showed an increased risk of gestational hypertensive disorders (odds ratio, 1.37; 95% confidence interval, 1.21 to 1.55) in women with epilepsy.[9] In a 2017 national cohort study in Sweden, the incidence of preeclampsia was 4% in women with epilepsy compared to 2.8% in the control group.[10] Exposure to different antiseizure medications was associated with different outcomes; lamotrigine and levetiracetam did not predispose to mild preeclampsia, whereas valproate was associated with an increased risk of mild preeclampsia.[11]

Folic acid Supplementation

During pregnancy, folate requirements are 5- to 10-fold higher compared to nonpregnant women, and adequate periconceptional folate status is essential for the structural and functional development of the fetal brain. Periconceptional folate is particularly important to women with epilepsy who are taking antiseizure medications, given the fact that several antiseizure medications, especially those that induce cytochrome P450 enzymes, are known to decrease folate levels.[12] Periconceptional folic acid supplementation at a dose greater than 400 mcg/d is associated with better neurodevelopmental scores across a variety of long-term cognitive variables in children of women with epilepsy at 6 years old.[13] The American Academy of Neurology practice guideline recommends 0.4 mg/d to 4 mg/d of periconceptional folic acid supplementation.[14,15]

Antiepileptic drugs and depression during pregnancy

Analysis of data from 2039 pregnancies in the Raoul Wallenberg Australian Register of Antiepileptic Drugs in Pregnancy followed during pregnancy. Patient-recognized depression occurrence rates during pregnancy were a little lower rather than higher in seizure-affected than in seizure-free pregnancies (5.67% vs 6.41%), though higher in antiepileptic drug-treated than antiepileptic drug-untreated pregnancies (6.24% vs 5.26%; RR = 1.185, 95% CI 0.612, 2.295). Logistic regression analysis showed that carbamazepine dosage had a statistically significant relationship with a decreasing rate of patient-recognized depression occurring during pregnancy and topiramate dosage with an increasing rate. Carbamazepine and topiramate both have established potentials for causing teratogenesis, and it is possible that the replacement of carbamazepine with a less teratogenic antiepileptic drug, for example, levetiracetam, might result in any subsequent depression that occurs in pregnancy being inappropriately attributed to the newly introduced agent.[16]

Status epilepticus in pregnancy

Status epilepticus in pregnancy represents a life-threatening medical emergency for both mother and fetus. Prompt treatment of status epilepticus during pregnancy is paramount, and a multidisciplinary

team is needed. Benzodiazepines are the drugs of choice for status epilepticus in pregnancy. Levetiracetam and phenytoin represent the most suitable second-line agents. Valproic acid should be administered only if other antiepileptic drugs failed and preferably avoided in the first trimester of pregnancy. For refractory status epilepticus, anesthetic drugs are needed, with propofol and midazolam as preferred drugs. Magnesium sulfate is the first-line treatment for status epilepticus in eclampsia. Termination of pregnancy via delivery or abortion is recommended in case of failure of general anesthetics.[17]

Breastfeeding and antiepileptic drugs

Patients are often concerned that exposure to antiepileptic drugs via breast milk could potentially affect their children's development. Valproate, phenobarbital, phenytoin, and carbamazepine are not thought to penetrate breast milk at a clinically important level, whereas lamotrigine, levetiracetam, primidone, gabapentin, and topiramate probably penetrate breast milk in potentially clinically important amounts. Although further studies of exposure to other newer antiepileptic drugs via breast milk are necessary, women with epilepsy should be encouraged to breastfeed their children irrespective of antiseizure medication treatment.[18]

Contraception

Many forms of contraception are available to women with epilepsy. The most common reversible contraceptive methods include oral contraceptives, the dermal patch, depot medroxyprogesterone acetate injection, vaginal rings that contain hormonal steroids with combined progesterone and estrogen or progesterone alone, copper T intrauterine device (IUD) or levonorgestrel IUD, spermicides, and mechanical barriers such as condoms or a diaphragm. Generally speaking, long-acting reversible contraceptives such as contraceptive implants and IUDs have the lowest contraceptive failure rates of around 1%. The least effective methods are condoms, withdrawal, and fertility awareness-based methods, which have the highest risk of contraceptive failure (ranging from 13% to 20%). The failure rate for all hormonal contraceptive methods combined has been reported to range from 6% to 9% in the general population.[19,20]

CONCLUSION

The findings of these studies encourage the consideration of levetiracetam or lamotrigine monotherapy for women with epilepsy who are pregnant and strongly discourage the consideration of the older antiepileptic drugs, especially phenytoin and phenobarbitone, and most especially valproate. These considerations also apply to all women with epilepsy of childbearing age because it may not be easy to change antiepileptic drugs when pregnancy is planned and because pregnancy is often unplanned. If the antiepileptic drug concentration changes by more than 25% compared with the reference concentration, dose adjustment is advised, and therapeutic drug monitoring is required for women with epilepsy taking antiepileptic drugs to prevent uncontrolled seizures.

Conflict of Interest

The authors declare no conflicts of interest relevant to this article.

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