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An Update on Treatment of Epilepsy during Pregnancy

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Abstract
Prevalence of epilepsy in pregnant women has been estimated at 0.3–0.7%. Even though this neurologic condition is uncommon, epilepsy poses significant clinical difficulties during pregnancy. The difficulty in treating pregnant women who have epilepsy is striking a balance between the benefits to the mother of continuing an effective treatment regimen and the hazards to the fetus from drugs with known teratogenic potential or to the mother from inadequate management of her epilepsy. The evolving ideas discovered from studies in women with epilepsy can be applied to a much larger group of pregnant women to improve child outcomes while maintaining maternal disease control, as the number of Anti-epileptic drug prescriptions has significantly increased in reproductive-aged women with a variety of neuropsychiatric indications. People over 55 are more likely than younger people to have epilepsy, and they are also more likely to experience consequences including stroke, brain tumors, or Alzheimer's disease [5]. Epilepsy affects between 0.5% and 1.0% of expectant mothers. Around 50–70 new cases of epilepsy are diagnosed annually per 100,000 persons in wealthy countries, with a prevalence of 5–10 instances per 1,000 people. Compared to non-pregnant women during the same time periods, pregnant women experienced dosage modifications for antiepileptic medications more frequently. Lamotrigine and levetiracetam were the two most frequently recommended polytherapy combinations, as well as the two most frequently used monotherapies, according to the ILAE Guidelines. While supplementing with folic acid during pregnancy, no more than 5mg should be used daily. Particularly for polytherapy, other AEDs were used much less frequently and inconsistently. The majority of participants struggled with making the decision of whether or not to breastfeed while taking Anti-Epileptic drugs

Key words
Epilepsy, Preconception counselling, Pregnancy, breast feeding and contraception, Anti- Epileptic drugs.

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I. Background

Epilepsy is a condition of the central nervous system that deactivates some brain functions, resulting in seizures, odd behavior, and a loss of awareness and sensations. However, about 1.5 million women—or 1 in 200 women of reproductive age—are plagued with epilepsy, making it one of the most prevalent neurological diseases during pregnancy. Typically, a woman's gestational period alters her physiological state and has an impact on her pharmacokinetic parameter [1]. In the entire world, epilepsy is ranked as the fourth most prevalent neurological condition, and each year, it appears to affect roughly 48 out of every 100,000 people (according to epilepsy foundation, 2014). According to a 2019 World Health Organization report, 50 million individuals worldwide suffer from epilepsy. Between 1990 and 2016, the prevalence of epilepsy with no known cause rose to 6%. Any age can be impacted by and acquire epilepsy [3]. Children, specifically those between the ages of one and two, are most likely to develop new instances of epilepsy [2]. People over the age of 55 are more likely to have epilepsy than younger people, and they also have a higher risk of developing complications including stroke, brain tumors, or Alzheimer's disease [5]. An estimated 0.5% to 1.0% of pregnant women have epilepsy. In affluent nations, there are roughly 50–70 new cases of epilepsy per 100,000 people each year, with a prevalence of 5–10 cases per 1,000 people. A significant portion of cases, with an incidence of 100–190 cases per 100,000 people year, are found in the developing countries. Pregnant women have a 3.33 per 1000 prevalence of active epilepsy [3, 5]. The majority of pregnant epileptic women experience successful pregnancies, however there is a higher risk for both the foetus and the mother as compared to the general population at large. Antiepileptic medication exposure or administration during gestation periods puts the foetus in the womb at danger. Sometimes the Anti-epileptic drug is required to monitor pregnant women with epilepsy because seizures during this time can be harmful to both the mother and the foetus. In order to reduce the risk of

foetal growth from the influence of antiepileptic drugs and maintain a balance between seizure episodes, there are serious challenges for women with epilepsy during their gestation period and during childbirth. For these reasons, many studies have been evaluating the use of antiepileptic drugs. Contrary to women who are not on anti-epileptic medications, pregnant epileptic women have a higher risk of abortion [1]. When compared to women with epilepsy who are not pregnant, those who have epileptic pregnancy experience the same frequency of seizures. The same study from Boston, USA, stated it [7], and women with epilepsy during pregnancy also had a high chance of miscarriage. Another Canadian study demonstrating that polytherapy was more effective at identifying malformations than monotherapy. Compared to women with epilepsy who are not receiving treatment, malformation rates in valproate monotherapy and polytherapy are greater [8]. Both monotherapy and polytherapy are prescribed while being closely watched, with monotherapy being less harmful than polytherapy. Compared to the non-exposed women with epilepsy, abnormalities were found in the AED-exposed epileptic women [8]. Pregnancy-related new-onset seizures were uncommon, and the majority of the women who experienced them also experienced epileptic seizures after giving birth [9]. Pregnant women with refractory epilepsy run the risk of obstetric and neurological complications. Without treatment, the women's risk for seizures has doubled. Women with epilepsy encounter seizures that appear three or four times more frequently to continue to have seizures throughout pregnancy than women whose seizures were properly controlled prior to pregnancy. Lamotrigine and levetiracetam were used for monotherapy, and they were also frequently combined for polytherapy [10]. The medicine used to treat epilepsy during pregnancy has a significant impact on the combination diagnosis of autism, congenital deformity, and psychiatric condition in the foetus. There is also evidence that utilizing polytherapy during pregnancy causes more foetal deformity than using monotherapy, while monotherapy use during pregnancy in women with epilepsy causes mild malformation and requires monitoring [11]. After the gestation stage, new epilepsy conditions can continue to develop in pregnancy. Even when epileptic women stop using Anti-epileptic drug's during pregnancy, there is still a risk of epilepsy, although the risk of foetal deformity has diminished.

Predicting seizure control during pregnancy

According to numerous studies, the ability to control seizures prior to becoming pregnant is the best indicator of how seizure-free the subsequent pregnancy will be. Only 20 percent of their pregnancies continued without seizures [14]. The roles of the individual drugs in this situation have not been clarified, and the drug combinations may have been used because the women involved epilepsies had not been controlled by antiseizure medication monotherapy. Several studies have found that seizure disorders were more likely to worsen during pregnancy if antiseizure medication combinations had been used in treatment. Data from the Australian Pregnancy Register showed that having a seizure disease without receiving antiseizure medication prior to becoming pregnant increased the risk of having a pregnancy impacted by seizures [19].

Pre conceptional counselling

Preconception counselling is an essential component of holistic management of women with epilepsy and should cover information on risks related to epilepsy and pregnancy, potential side effects from oral contraceptive therapy, and suggested folate supplementation. Significant foetal malformations are independently associated with low serum folate levels in epileptic women. The Medical Research Council (MRC) vitamin study showed that folic acid supplementation (4 mg per day) starting before pregnancy was associated with a 72% reduction in the incidence of neural tube defects in women at high risk due to a prior preterm birth. However, this study did not include women with epilepsy [15]. Published clinical recommendations for the dosage of folate supplementation in epileptic women vary and are not clear. According to 2009 recommendations from the American Academy of Neurology and American Epilepsy Society, there is not enough research to say whether doses more than 40.4 mg provide stronger protective advantages. In contrast, the American College of Obstetricians and Gynecologists advises women who run the risk of having children with neural tube abnormalities should take 4.0 mg of folic acid daily (including women 5taking ant seizure drugs) [14]. The greater folic acid intake has not been linked to any negative effects. Pre- conception counselling aims to optimize Anti-Epileptic drug therapy and ensure a minimum seizure-free window before conception [11]. In relation to 'Anti-Epileptic drugs, the majority of the evaluated studies confirm that valproic acid use should be avoided whenever possible in women of reproductive age. It is advisable to transition from Valproic acid along with other Anti-Epileptic drugs to monotherapy with safer alternatives. Levetiracetam and lamotrigine are the best options for women who want to get pregnant because they are both relatively less teratogenic. [20]

Breastfeeding and contraception

All anti-seizure medications can be detected in breast milk, with maternal plasma levels reportedly ranging from 5–10% with Valproic acid to 90% with ethosuximide. However, according to the majority of experts, using anti-seizure medication is generally not a contraindication to breastfeeding because the benefits

are likely to exceed the risks, and women with epilepsy should be advised of this [17]. Therefore, injectable contraceptives and long-acting contraceptive techniques such intrauterine devices are favored means of contraception in these women. In India, post-placental implantation of an intrauterine device appears to be a safe and effective procedure. Women should be aware that the effectiveness of hormonal contraceptives may be decreased when taken with Anti-Epileptic drugs, particularly those that stimulate the hepatic cytochrome P-450[16]

Female sex hormone effects

Progesterone has an antiepileptogenic impact while estrogens have a pro-epileptogenic effect. In the luteal phase of the menstrual cycle, progesterone medication did not successfully control women's catamenial seizures. Daily salivary progesterone levels in women with catamenial epilepsy during the menstrual cycle. They discovered that the plasma antiseizure medicine concentration tended to decrease in relation to dose during the premenstrual level fall [17]. This finding suggests that the drug concentration decline may have been a significant correlate of the prevalence of catamenial seizures.[16] The occurrence of catamenial epilepsy, as previously indicated, was recognized before potassium bromide, the first reasonably effective antiseizure drug, came into use, therefore it cannot be the complete explanation.[14] There is a correlation between the frequency of seizures during pregnancy and the amounts of circulating sex hormones; seizures were more frequent in areas where estrogen levels were higher and progesterone levels were lower[16,17].

Neural defects caused by using antiepileptic drugs

Because of its potential teratogenicity when used by pregnant women, various Anti-Epileptic drugs have been studied. Given that it is known that Anti-Epileptic drugs cannot be stopped when a woman is pregnant, this problem requires extensive discussion. These Anti-Epileptic drugs such as phenytoin, valproate, phenobarbital, carbamazepine, lamotrigine, and Topiramate—are covered in this study. Given that maternal mortality occurs in 30% of pregnancies and foetus mortality occurs in 50% of pregnancies, the statistics for pregnant women who use Anti-Epileptic drugs are very serious. [18] Despite these disadvantages, most medical professionals' advice using Anti-Epileptic drugs while pregnant. This is due to the fact that, in general, pregnant women with epilepsy give birth normally, and the children are born without any anatomical flaws. However, the likelihood of the infants being delivered with birth abnormalities is still higher than in a typical pregnancy.

Monitoring Serum Levels of AEDs

Due to modifications in pharmacokinetics during absorption, metabolism, or excretion, serum concentrations of the majority of Anti-Epileptic drugs may alter during pregnancy. During Pregnancy the usage of drugs such as Lamotrigine, Levetiracetam, or Oxcarbamazepine Concentrations have been monitored to fall by up to 30–50%. Lower medication levels could cause seizures to become more severe. Therefore, it is advised to check the serum levels of these medications before becoming pregnant, at least once during each trimester, and in additional instances like when seizure control is insufficient or when unpleasant symptoms manifest [19]. Taking Lamotrigine into account, this Anti- Epileptic drug had a penetration ratio of 0.68 for amniotic fluid, 0.92 for umbilical cord, and 0.77 for breast milk. Once more, these findings might suggest therapeutic medication monitoring [19, 20]. A double-blind randomized trial was conducted to assess two prenatal management approaches: clinical characteristics monitoring or therapeutic medication monitoring. In the first approach, practitioners had access to clinical data as well as monthly serum Anti-epileptic drug concentrations. In the second strategy, Carbamazepine, Phenytoin, Lamotrigine, and Levetiracetam Anti-epileptic drug dosage adjustments were solely made based on clinical outcomes. The outcomes unmistakably show that, following randomization, there was no significant difference between the two groups in the timing of any seizures or the time before the first seizure [23]. The only difference between maternal and newborn outcomes was higher cord blood concentrations of Lamotrigine and Levetiracetam. However, there were no consequences for the mother or the fetus as a result of increased exposure to these Anti-epileptic drugs. These findings suggest that therapeutic Anti-Epileptic drug monitoring may not be required in epileptic pregnant women. [20, 23]

Treatment plan for seizures during pregnancy

i. Drugs considered safe Phenytoin, Valproic acid, Carbamazepine.

ii. Drugs considered moderately safe: Lamotrigine, Oxcarbamazepine, Levetiracetam, Topiramate, Gabapentin, Pregabalin, vigabatrin, Tiagabine.

iii. Drugs Use with Caution: Primidone, Phenobarbital Benzodiazepines, Ethosuximide, Zonisamide, and Felbamate.

iv. No information available on some newer AEDs: Lacosamide, Esclicarbazepine.

Prophylaxis with Vitamin K

Anti-Epileptic drugs that are inducers of hepatic enzymes, such as Carbamazepine, Phenobarbital, primidone, Oxcarbamazepine, Topiramate, are competitive inhibitors of prothrombin precursors, posing a risk of hemorrhage into body cavities and brain in neonates. Such complications have a high mortality rate of up to 30% [21]. To reduce this risk, it is recommended that pregnant women using AEDs, that induce hepatic enzymes, be given vitamin K at a dose of 20 mg per day during the last two weeks before delivery, and that 1 mg of vitamin K be given to the newborns. Another study from United Kingdom, compared the influence of hepatic enzyme inducers on the risk of perinatal bleeding to that of other AEDs (Valproic acid, Lamotrigine, Levetiracetam, Pregabalin, Gabapentin, clonazepam). The study was conducted on 11,572 pregnant women with epilepsy. A considerable fraction of patients on enzyme inducers were supplemented with vitamin K before delivery. [24] Postpartum hemorrhage was evident in 2.6% in the group on enzyme inducers and in 3.6% in the group on other AEDs. The prevalence of neonatal bleeding did not differ significantly among the two groups. Also, data exist showing that prenatal vitamin K supplementation did not cause any significant difference in postpartum hemorrhage in women taking enzyme-inducing AEDs.

Folic Acid Supplementation

A dose of 5 mg/day of folic acid is advised for women who are considering becoming pregnant as well as during the first few months of pregnancy because clinical studies have demonstrated that folic acid supplementation helps prevent abnormalities in offspring of women using Anti- Epileptic drugs. Folic acid intake above 5 mg/day is not advised because it may lower the seizure threshold. [27]

II. Conclusion

First-time epileptic seizures do happen during pregnancy, but they tend to happen in pregnant women who already have epilepsy. Most of the participants who developed new-onset seizures during pregnancy also experienced seizures after giving birth. The proportion of women with seizures who experienced more awareness-impairing seizures during pregnancy than after giving birth. Antiepileptic medication dosage adjustments happened more frequently in pregnant women than in non-pregnant women during the same time periods. As per ILAE Guidelines, Lamotrigine and levetiracetam were the two most frequently prescribed polytherapy combinations as well as the two most frequently utilized monotherapies. Folic acid supplementation should be advised during pregnancy but it should not exceed 5mg. Other AEDs were used significantly less frequently and inconsistently, particularly for polytherapy. The majority of participants had trouble deciding whether or not they should breastfeed while using AEDs is a difficult choice. Close regular monitoring of mother-infant health would also help to lessen the mother's concern and minimize serious adverse effects. Breastfeeding is safe and should be recommended for the period of at least 6 months, preferably 12 months.

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