

The Use Antiepileptic Drug (AED) during Pregnancy

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Abstract:

In the world, Epilepsy is recognized as the commonest serious neurological disorder. Women with epilepsy (WWE) experience several gender-related social and physical problem. During pregnancy, the main concerns linked with epilepsy that consist of maternal and fetal risk from uncontrolled seizures, and harmful effects of treatment on the development of offspring. In pregnant women, increasing the risk of safety whenever an antiepileptic drug is taken by patients but this drug is not completely safe to use in pregnancy as the risk of fetal abnormality is increased. Before conception, planning should be done for managing the women's epilepsy during pregnancy. Without medical advice, the occurrence of an unexpected pregnancy should not be treated with sudden cessation or alteration of an antiepileptic drug. In this case, should be used the smallest effective dose of a drug with a low risk of teratogenicity. During pregnancy, doses may need adjustment as the pharmacokinetics of some drugs. In this paper, discussed about the using the antiepileptic drug during pregnancy and safety of antiepileptic drug use during pregnancy.

Keyword: Antiepileptic drug, Teratogenicity, Epilepsy, Pregnant women

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Introduction

Epilepsy is the most common chronic neurological problem in which, pregnant women have a serious and potentially life-threatening condition for both mother and infant and required the continuous pharmacological treatment throughout pregnancy. With epilepsy, most pregnant women need to take at least one antiepileptic drug (AED) and this drug is prescribed to reduce the severity of epilepsy or help to manage the conditions such as psychiatric disorders, pain, and migraine. Women taking AED have a risk of teratogenicity and miscarriage, including a 4-8% chance of giving birth to a child with major congenital malformation (CM) because these agents can be transferred from placenta to fetus. Teratogenicity of AED was first documentation in the 1960s, in pregnant women with epilepsy, the use of many first-generation AEDs (Valproate) has been studied extensively.

In pregnancy, use of the antiepileptic drug for safety purpose involves the pregnant women in her own right; the fetus while in her womb, and during its subsequent extra-uterine existence as a neonate and infant. The safety of antiepileptic drugs during pregnancy is not significantly different from the safety of these drug in normal women, except in case of normal women, these drugs are affecting on the pregnant lady and drugs effect on the foetus in utero and afterward. But in recent years, antiepileptic drugs have been used in increasingly to treat the disorders other than epilepsy.

In the United States, approximately 1.3 million women with epilepsy are in their active reproductive years and give birth to 25,000 infants each year. With the favorable outcome, most women with epilepsy will have a normal pregnancy but there are increased fetal and maternal risk compared to the general population. On developing offspring, fall the effects of ADE include both anatomic teratogenic and neurodevelopment significances. Women with epilepsy have offspring on AEDs that are at an increased risk for intrauterine growth retardation, major congenital malformations, minor anomalies, microcephaly, cognitive dysfunction, and infant mortality. "Fetal anticonvulsant syndrome" is a term that is used to include various combination of these findings.

In pregnant women, treatment of epilepsy by the use of monotherapy with most effective AED for the women's epilepsy type at the lowest effective dose. Valproate drug falls the adverse effect on developing fetus due to which it should be avoided. During pregnancy, epilepsy should be managed by the requirement to weighing the possible adverse effects of AEDs on the fetus against the effects of seizures on

the mother and the fetus. During pregnancy, maintaining the balance between adequate seizure control and teratogenic risk of ADEs that is a major challenge for neurologists. Over the years, the efficacy of AEDs may have changed through a better understanding of their pharmacokinetic properties during pregnancy and their efficacy in the treatment of different types of seizures.

Seizures Control during Pregnancy

In several studies, investigated the effect of pregnancy on the course of epilepsy from the most of selected specialist epilepsy clinics, probably including a preponderance of patients with difficult-to-treat seizure disorders. In which, first check that is present or not, if there appears to be little or no evidence that antiepileptic drug use in pregnancy produces additional safety concerns for women involved and result come from decreased control of her epileptic seizures. Since 1857, effective antiepileptic drug treatment has been available and for many years, it has been little published on untreated epilepsy in pregnancy.

In case of during lack of control of epileptic seizures, could expose the pregnant women to the risk of physical injury and possible death during seizures. Seizures should be controlled during second and third trimester as compared to the first trimester. With epilepsy, loss of seizure control could lead to psychological harm to the woman in addition to physical injury that may result in reduced social activities and opportunities and may impair her quality of life. A number of studies have to show since the mid-1970s that as pregnancy progresses, steady-state plasma concentrations of antiepileptic drugs tend to fall unless the drug doses are increased. Involved may factor in producing this fall appear to be:

- The unmetabolized drug's increasing the renal clearances because of the physiological increase in glomerular filtration rate that begins early in pregnancy which phenomenon is of greatest importance for an antiepileptic drug that undergoes relatively little or no metabolism in the body.
- Increased biotransformation, because during pregnancy, increased circulating levels of female steroidal sex hormones that induce the formation of the cytochrome P (CYP) 450 isoenzymes and glucuronosyl transferases which play the main roles in eliminating the antiepileptic drug.
- By increasing the maternal extracellular fluid, womb, placental and foetal volumes due to which

dilutional effect was occur during pregnancy and in late pregnancy, an effect offset to an extent when plasma albumin concentration fall, so that there is an increased concentration of unbound (biologically active) drug that is relative to the total drug in plasma.

By these factors, decreases in plasma antiepileptic drug concentration between the individual drug and stage of pregnancy. By renal excretion unmetabolised, decreases tend to be relatively small for agents that are cleared from body predominantly and are larger for drugs cleared mainly through biotransformation. Seizure control tends to correlate with plasma antiepileptic drug correlations due to which it raises the possibility that antiepileptic drug doses are adjusted, falling circulating concentrations of antiepileptic drugs in pregnancy may explain any deterioration in seizure control that occurs. If antiepileptic drug doses are adjusted during and after pregnancy, then clinical impression has been developed, so that maintaining the concentration of plasma drug at their pre-pregnancy values in the individual, seizure control is unlikely to deteriorate. In most women, indicated the pregnancy does not appear to influence seizure control by various studies. In seizure control, women who experience changes can be divided into two approximately equally sized groups, the first one is improvement and second is deterioration.

Deficiency of vitamin K in Foetus

In the first couple of neonatal days in babies, bleeding diathesis was manifested and who had been exposed during pregnancy to antiepileptic drugs such as phenytoin and phenobarbitone. CYP450 isoenzymes have induced these drugs and thought that this induction caused increased metabolic inactivation of vitamin K, resulting in impaired vitamin K-catalyzed synthesis of blood coagulation factors. Vitamin K should be given in more or less amount to women with an antiepileptic drug that is treated as seizure disorders during childbirth and it is given to the neonates immediately after birth. This phenomenon may have been prevented from a drug associated bleeding problem. According to recent research, increasing replacement of these older antiepileptic agents with more introduced non-inducing drugs such as vitamin K, it may cease to any issue during pregnancy but vitamin may be administrated to neonates when indicated.

According to National Health and Medical Research Council Guidelines (2000), all babies at birth are given 1mg intramuscular vitamin K₁ or a course of oral vitamin K₁ and maternal should be taken 10mg/day oral vitamin K₁ for one prepartum and when enzyme-

inducing antiepileptic drugs are prescribed because these drugs are predisposed the baby to hemorrhagic disease of the newborn.

Pharmacokinetic (PK) factors

During the gestation period, a range of physiology changes may alter the pharmacokinetic (PK) of AEDs. By increasing the plasma volume and total body water that may lead to increased volume of distribution and thus reduced AED serum concentration. Serum albumin concentration may also reduce by increasing plasma volume which may affect AED protein binding and plasma clearance. By increasing the renal blood flow and glomerular filtration rate, may reduce the serum concentrations of AEDs predominantly eliminated through the kidneys. Some other factors may affect the PK of AED which are less well documented such as changes in gastrointestinal motility/drug absorption, and altered biotransformation capacity. Serum concentration influenced by a large number of factors, as well as the marked inter-individual differences both in drug disposition and seizure control, make clinical reality anything else than simple. In pregnancy, PK of antiepileptic drugs may change and doses have to balance the risk of seizures with minimizing the risk of harming the fetus.

Valproate (VPA)

Substantial risk of major malformations has to be seen in four pregnancy and numerous smaller studies that including spina bifida when valproate is used as monotherapy or with other drugs. After delivery, total VPA serum concentrations may decline by 50% and increase to pre-pregnancy levels within one week. In serum albumin concentrations, VPA is highly protein bound and hence susceptible to pregnancy-induced reduction. Accordingly, the unbound fraction has been shown to be inversely correlated to serum albumin concentration. It is a pharmacologically active and free fraction of a drug, this may outweigh the decline in total VPA serum concentrations. With increasingly total VPA serum concentrations, then increasing free fraction over-proportionally. In nine pregnancies a decrease of 39% of total levels was found, while unbound levels increased by 25% at delivery. Dose increase had taken place in four of the patients. Teratogenesis disease has been reduced in case of valproate dose that reduces to a minimum during pregnancy, the prepartum effective dose may need to be re-established before the onset of labor.

Lamotrigine (LTG)

LTG has a relatively low degree of protein binding (55%) and is unlikely to be considerably affected by

changes in serum albumin concentrations. However, LTG is extensively metabolized, mainly to LTG-N2-glucuronide by uridine-diphosphate glucuronosyltransferase (UGT). In the last trimester of pregnancy, its apparent clearance that increases to at least the double compared to baseline, by 40-60% dose-normalized serum concentration may be reduced in the third trimester, returning to non-pregnant levels within 1—2 weeks postpartum. When LTG serum concentrations fall then effect is less pronounced in women on enzyme-inducing or inhibiting co-medication, recommending an enhanced rate of glucuronidation as the underlying mechanism. During pregnancy, an increased LTG-N2-glucuronide/LTG serum concentration ratio has recently been demonstrated. In the first trimester of pregnancy, exposure to lamotrigine may cause an increased risk of oral clefts.

Carbamazepine (CBZ)

According to the extent study, carbamazepine increased with a risk of structural birth defects including spina bifida. In the third trimester, plasma clearance increases during pregnancy with a maximum and binding the protein is 70%. Its serum concentration may decline by over 40, but in the case of an unbound drug, it may be less affected. CBZ has a pharmacologically active metabolite, carbamazepine-10, 11-epoxide. During pregnancy, the ratio of epoxide metabolite to CBZ serum concentrations usually increases. Although not in a predictable manner.

Phenytoin (PHT)

With epilepsy, PHT is used less frequently in women and produce an increase in major malformations. With a fall in plasma concentrations and possible loss of seizure control, a marked increase in the clearance of phenytoin in pregnancy. When a higher dose is required is to determine the regular monitoring of plasma concentrations throughout pregnancy. Prevent phenytoin toxicity with the help of monitoring the postpartum. From the start of pregnancy, PHT serum levels decrease and may fall by more than 60% in the third trimester and returning to pre-pregnancy levels within a few weeks after delivery. Still, a clear-cut relation between total serum levels and seizure control of PHT has not been established and this may be related to changes in its free fraction. It is highly protein-bound, which make it susceptible to change in plasma concentration.

Phenobarbital (PB)

Phenobarbital serum levels decrease during pregnancy. According to this paper, total serum

concentrations declined by 55% with the sharpest fall during the first trimester. Unbound levels were a decline in the case of protein binding that is relatively low but considerable inter-individual variations have been demonstrated.

Levetiracetam (LEV)

During pregnancy, LEV drug has been used and its teratogenic risk is unknown and it appears to be a substantial increase in clearance and a linked fall of blood concentrations. If this is linked with a loss of epilepsy control, it is not yet known. Serum observing is not currently available, but may prove helpful in clinical practice. In blood, one-third of an oral dose is metabolized by hydrolysis and in urine, two-thirds are usually found unchanged. The underlying mechanism is unidentified. Both increased renal blood and/or increased peripheral hydrolysis flow are possible.

Topiramate (TPM)

TPM is metabolized in small proportion and up to 40% of an oral dose is eliminated unchanged through the kidney. Therefore, a pregnancy-related increase in renal blood flow might lead to an increased renal clearance and a decline in TPM serum concentrations.

Oxcarbazepine (OXC)

OXC is quickly metabolized to the pharmacologically active, monohydroxycarbamazepine (MHD-OXC) after oral intake, which is eliminated as a glucuronide. The protein binding of MHD-OXC is less than 50%. During pregnancy, this serum concentration of MHD was at least 36% lower, compared to pre-or post-pregnancy values, respectively.

Gabapentin (GBP) and pregabalin (PGB)

Through the kidneys, GBP and PGB are not metabolized and are eliminated unchanged. Supposedly, an increased glomerular filtration rate may then lead to reduced serum concentrations.

Zonisamide (ZNS)

ZNS is only 60% protein-bound and undergoes extensive biotransformation. Increased glomerular filtration and decreased serum albumin concentrations rate would not be expected to induce dramatic changes in the PK of ZNS. The increased volume of distribution is the other pregnancy-related changes that might affect ZNS serum concentrations.

Newer AEDs

In the newer generation of AEDs, consists of a large number of basically diverse compounds that may have to demonstrate teratogenic effects in preclinical animal

experiments. None of the agents has been sufficiently tested during human pregnancy with the possible exception of LTG and assess safety or teratogenicity. According to this paper, the most recent research from LTG pregnancy registry is based on 414 first-trimester monotherapy exposures and its malformations rate was 2.9%. Included all common AED category in reported birth defects and were not of a consistent pattern.

Review of Literature

Kulaga et.al 2011, stated that 0.28% of pregnant women use AED during pregnancy. The majority of women with epilepsy, taken the monotherapy during pregnancy recommended that there is recognition of the importance of both mother and fetus of continued control of symptoms of epilepsy during gestation. Prior to pregnancy, 12% of women treated with epilepsy and not receiving the AEDs during gestation periods. During the gestation period, if pregnant lady used an AED polytherapy treatment, then it is more likely to be wellbeing recipients or attends neurologist visits more normally in the 12-month period prior to the first day of gestation than those on AED monotherapy or no therapy. During pregnancy, carbamazepine has been shown to be a comparatively safer choice for control of epileptic seizures. If the first trimester of pregnancy used the valproate shown to hold teratogenic.

Widnes, Schjøtt and Granas 2012, dictated that to avoid seizures, pregnant women with epilepsy (WWE) were using confidently AEDs, while dose adjustments linked with pregnancy increased perceived risks of teratogenicity or seizures. The women were satisfied with follow-up the medicine and treatment that are provided by physicians and neurologist. It has some strategies that may also be relevant for medicines information to pregnant women with chronic diseases that provide balanced presentations of benefits and risks both of AEDs and other medicines to achieve satisfactory health of fetus and mother.

Díaz et.al 2012, in this study, the risk of malformations overall linked with first-trimester exposure to specific AEDs that have ranged from 9.3% for valproate to 2.0% for lamotrigine. In case of phenobarbital, valproate and topiramate users, the risk of oral clefts was more than 10 per 1,000 for infants exposed, which is higher than expected based on any reference population (approximately 1 per 1,000 births). The teratogenicity of valproic acid is well established. The first-trimester exposure to valproic acid increases the risk of neural tube defects from approximately 1 per 1,000 to 10 per 1,000 births. Oral clefts, cardiovascular and urogenital defects are

associated with phenobarbital and these defects have also been reported after phenytoin therapy.

Clemow et.al 2014, dictated that in pregnancy, factors leading to a lack of data-supported decision making on medication use included restricted research approaches, limitations of current research methodologies, research standards, lack of data, fragmentation of existing data, poor patient communication and inconsistent application of findings to clinical practice. Risk-based approaches that do not consider the benefits of treatment and litigation concerns are cultural factors that also inhibit the provision of proper medical guidance.

Bech et.al 2014, in this paper, no increasing the risk of spontaneous abortion during pregnancy when women with epilepsy who take antiepileptic drugs. According to data, the risk of fatal death is low in pregnant women with epilepsy can continue antiepileptic drug treatment. This studies indicated that women with epilepsy treated with a high dose of an antiepileptic drug that might have an increased risk of spontaneous abortion, especially when using high doses of clonazepam, carbamazepine, and valproate. This drug is harmful effects on developing fetus including congenital malformations and adverse effects on neurodevelopment.

Pem, Gupta and Khatik 2016, concluded that safe and unsafe medications during pregnancy are very important prospective of life as it carries the two lives conjoined for the certain period of time. Both mother and fetus should be safe, sound and grow healthy during that time period. It is very important for the one to be aware of the contraindications with the new discovery of the drugs during undergoing any medications. Majority of pregnant women that would not take a drug treatment as prescribed by a physician and neurologist as there is the same fear of harming the fetus as the main concern for mothers. It is important that risk and benefits of stopping treatment to be explained and informed properly.

Veroniki et.al 2017, stated that this analysis recommended that the newer generations of AEDs, lamotrigine, and levetiracetam, were not linked with statistically significant increased risk to congenital malformations compared to control and less likely to link with children experience cardiac malformations than control. Increasing the risk of malformations for ethosuximide, valproate, topiramate, phenobarbital, phenytoin, carbamazepine, and 11 polytherapy.

Ferri et.al 2018, stated that with generalized epilepsy and focal epilepsy, the percentage of patients are similar in both periods analyzed and consistent with the percentages observed in the EURAP registry. This

study shows a change a pattern of LTG treatment, with fewer patients with generalized epilepsy receiving the drug in the more recent period than in the first. This type of drug is not effective for generalized myoclonic epilepsy. According to Australian registry, AEDs are more effective for managing epilepsy in pregnant women than the new AEDs (LTG, TPM, and LEV) in the whole series as well as in the group of patients treated since 2008. This study also finds that a decrease in the use of CBZ and a lesser extent to VPA and use of LEV increased significantly.

Conclusion

Antiepileptic drug plays an important role with women epilepsy because when these drugs are received by pregnant women, it is a better than 90% chance that the child will be normal. But women with epilepsy have increased risks for fetal and maternal implications, these risk can be considerably reduced by the selection of AED treatment regimens. The most effective drug is valproate that reduced the risk of epilepsy and therapeutic dilemma. Without complication, most infants whose mothers are taking the antiepileptic drugs can be successfully breastfed. In highly protein bound and unbound concentrations may be less affected than total levels

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