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THE CHALLENGE OF TREATING EPILEPSY IN PREGNANCY: MATERNAL AND OFFSPRING PERSPECTIVES

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SUMMARY

Epilepsy is a common medical and social disorder and usually defined as a tendency to recurrent seizures. Freedom from seizures is the ultimate goal in treatment of patients with epilepsy. At the same time, the side effects of antiepileptic drugs (AEDs) should not outweigh the benefits of treatment. This is particularly important in epileptic women who wish to become pregnant. Those women have a higher risk for pregnancy-related complications. For babies whose mothers take AEDs, the risk of birth defects is 4 to 8 percent, compared with 2 to 3 percent for controls. The risk seems to be highest when multiple AEDs are taken, but without medication, uncontrolled seizures may deprive the baby of oxygen. Seizures can also increase the risk of miscarriage or stillbirth. By working with her physicians, a woman with epilepsy can become pregnant and have a happy outcome.

In the Sudan we lack national epidemiological studies using standardized definitions and case ascertainment methods on epilepsy as general and in pregnancy, but according to the WHO the number of people with epilepsy is high in most regions of the world. The mean number per 1000 population is 8.93 (SD 8.14, median 7.59). This knowledge is essential for the identification of needs and the planning of appropriate services. This a thorough review of more than 40 articles published over the last 10 years. However, it is not a complete reference for designing a protocol for the management of epilepsy in pregnant women. It aims at discussing current management of epilepsy and pregnancy, including the fetal outcome and teratogenicity of AEDs. It is part of a series mandated by the Gezira Epilepsy Care Program (GECP), to obtain baseline data for a community-adapted epilepsy education and awareness program.

Keywords

Epilepsy , pregnancy, fetal malformations, miscarriage, perinatal death, seizure, antiepileptic drugs, preeclampsia, eclampsia, neural tube defects, birth defects, teratogenicity, status epilepticus

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Introduction

The number of pregnant women with epilepsy has risen as seizures have been well controlled with modern pharmacotherapy. Up to 5% of pregnancies occur in epileptic women. The combination might seem risky. Some women who have epilepsy have menstrual irregularities and other gynecological problems that may make it harder to conceive.

Antiepileptic drug treatment, hormonal changes, and vitamin deficiency can affect seizure patterns, even for women who have had excellent seizure control in the past. These and genetic factors may increase the risk for birth defects in infants born to epileptic mothers.[1] Although this risk is not significant enough to avoid pregnancy, epileptologists advise attentive care for epileptic mothers. Regular and early prenatal care makes more than 90 percent of pregnant women who have epilepsy deliver healthy babies.[1]

Women who have epilepsy predisposed to a higher risk of pregnancy-related complications, including; vaginal bleeding during and after pregnancy, abruption placenta and preeclampsia. Difficulties during labor and delivery include premature labor, failure to progress, and an increased rate of cesarean sections.[2]

Every woman reacts to pregnancy differently with respect to seizures frequency. Most epileptic pregnant women have no changes in seizures frequency, whereas, for a few, seizures become less frequent. Pregnant mothers with poorly controlled epilepsy have increased number of seizures. For most women, however, it's best to continue treatment during pregnancy to minimize the risks for her and her baby.[3] Women with epilepsy are potentially at risk of fetal malformations, which is further increased with the use of antiepileptic drugs (AEDs).[4]

Reducing AEDs dosage or discontinuing medication is unsafe because uncontrolled seizures can reduce uterine oxygen or blood supply, which puts both the woman and the developing fetus at risk.[5] Also, changes in treatment can immediately alter the concentration of medication in the body, which may lead to sudden changes, especially during pregnancy that may lead to status epilepticus, where the risk to a mother and a developing fetus is high. Therefore, any decision to discontinue AED therapy during pregnancy, particularly if a patient has not experienced seizures for several months, should be made at the discretion of the treating physician only.[6]

EPILEPSY AND PREGNANCY

Incidence of Epilepsy and Pregnancy

Up to 5% of pregnancies occur in epileptic women and approximately 20% of women with epilepsy experience an increase of episodes during pregnancy. Pregnancy affects each woman who has epilepsy differently. Some experience seizures only while giving birth. Whereas, some women experience fewer seizures than normal while pregnant.[7]

Effect of Pregnancy on Seizures

During pregnancy, one quarter to one third of women with epilepsy have an increase in seizure frequency despite continued use of AEDs. Certain physiological changes that occur during pregnancy may lead to increased frequency, and difficulty control of seizures in some women with epilepsy.[8] Uncontrolled seizures, particularly generalized tonic-clonic episodes, are hazardous during pregnancy and discontinuing AEDs may pose a greater risk for both mother and fetus than the possible adverse effects of the medication. A theoretical risk of abruptio placentae exists, possibly leading to fetal hypoxia or death. Furthermore, the risk of maternal aspiration can lead to maternal hypoxia, which can also lead to fetal hypoxia. Evidence indicates seizure frequency increases during 17-33% of pregnancies.[9] This is usually in the last trimester or peripartum. Several possible etiologies have been proposed for this occurrence. These changes include;

increased hormone production, altered eating habits, increased stress, altered metabolism of AEDs due to increased blood volume leads to increased volume of distribution. Severe nausea and vomiting during early pregnancy may upset the balance as well.

Generally, sleep deprivation influences seizure frequency for those who suffer from epilepsy. A significant increase in seizure occurrence may result during pregnancy when sleep patterns change. Stress and changes in eating and sleeping habits may also contribute to more frequent seizure activity in some cases.[10]

Renal function increases during pregnancy, with a 50% rise in creatinine clearance, which impacts the metabolism of carbamazepine, primidone, and benzodiazepines. The increase in total blood volume and a concomitant rise in the distribution volume also lead to decreased levels of circulating AEDs. In contrast, the decrease in albumin and circulating plasma proteins likely increases the free component of the AEDs in serum.[11]

Many women are hormonally sensitive. Estrogen and progesterone increase naturally and steadily during normal pregnancy. Increased levels of circulating estrogen during pregnancy increase the function of the P-450 enzymes, which leads to more rapid hepatic metabolism of the AEDs.[12] Estrogen and progesterone hormones act in opposite ways in terms of electrical excitability of the brain. In experimental models estrogen increases the electrical activity of the brain by lowering the seizures threshold, whereas, progesterone elevates seizure threshold and may have an antiepileptic effect. Fluctuations in the levels of these hormones during pregnancy can make it more difficult for epileptic women to predict and control seizures. Adjusting the ratio of estrogen and progesterone isn't a substitute for AEDs, but hormone supplementation on top of regular seizure medicines really might improve things.[13]

Pregnant women may have decreased compliance with taking AEDs because of concerns regarding the effects on their fetuses. It is therefore very important to monitor levels closely during pregnancy and to adhere to prescribed treatment.[14] This needs frequent dosage adjustments to maintain seizure control. Serum levels of AEDs should be obtained at the end of each trimester. Plasma levels of unbound AEDs should be monitored closely throughout pregnancy and for at least 8 weeks following delivery, as it is common for levels to rise in the postpartum period. Free levels, for highly protein bound drugs such as valporic acid or phenytoin give a better indication of whether dose adjustments are needed.[15]

Rarely, some patients experience their first seizures during pregnancy. This can be a result of true gestational epilepsy, a rare syndrome of seizures occurring only during pregnancy. Patients with this syndrome have a variable presentation with single or multiple seizures in one or more of their pregnancies. It can also be a manifestation of epilepsy that may extend beyond the pregnancy.[16]The differential diagnosis should include eclampsia and preeclampsia and any possible etiology considered in the non-pregnant patient, including stroke, electrolyte abnormalities, tumor, trauma, drugs withdrawal, and epilepsy.[17]

Eclampsia is defined as one or more tonic-clonic seizures in a patient with preeclampsia which includes recently elevated blood pressure, proteinuria and elevated liver enzymes. Associated encephalopathy is related to vasoconstriction, cerebral oedema, micro-hemorrhages and disseminated intravascular coagulation. Treatment consists of control of hypertension, management of cerebral edema and control of seizures. Conventional AEDs, such as benzodiazepines or phenytoin, have been used, but magnesium sulphate had been found to be more effective and must be used as an initial therapy in hypertensive patients during labor.

Preparing for pregnancy

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More than 90 % of women with epilepsy will have normal, healthy infants. However, they are at greater risk for complications of pregnancy, labor and adverse pregnancy outcomes than women without epilepsy. Despite the great worries associated with pregnancy in epileptic women or who are trying to become pregnant, it had been confirmed that most women with epilepsy can and do have normal pregnancies.[17] Some well-documented risks are associated with taking AEDs while pregnant, but the answer usually is not to stop AEDs as maternal seizures have their own hazards such as induction of premature labor and miscarriage following a generalized tonic clonic seizure.[18]

Unplanned Pregnancies

Oral contraceptive failure increased four to five times in women with epilepsy taking certain anti-epileptic drugs (AEDs). This hormonal birth control failure is due to induction of estrogen metabolism and to a lesser extent progesterone metabolism by many AEDS, such as carbamazepine, oxcarbazepine, phenytoin, barbiturates and topiramate.[19]

Fertility and hormonal influences

Women with epilepsy have fewer children than the general population, with a fertility rate 25 to 33 percent lower than average. [20] Research has indicated that women with epilepsy have a higher incidence of menstrual irregularities, polycystic ovarian disease and reproductive endocrine disorders due to side effects of AEDs (e.g., valporic acid) or induction of sex hormone metabolism by hepatic enzyme-inducing agents.[20] A population-based study conducted in Iceland have contradicting results showing that there was no reduction in fertility, except when mental retardation or congenital neurologic impairment was present. They suggested that fertility may not be reduced by epilepsy or its treatment.[21]

Anti-EPILEPTIC DRUGS AND BREASTFEEDING

Breast feeding is beneficial; its immunological and nutritional value to the newborn infant is greater than that of formula milk. Many common AEDs cross the placenta, and may show up in breast milk at low levels, there is no evidence of harm to the newborns with the exception of valproate and, to a lesser extent, phenobarbital and phenytoin. If those mothers can avoid valproate, then there will be minimal adverse outcomes in their children.[22] AEDs, primidone, and levetiracetam were detected in breast milk at various clinically important levels. However, it has to be stressed that women should not stop taking any drug without consulting their physicians who have to weigh the potential risk of birth defects against the potential risk of uncontrolled seizures.[23]

FETAL CONGENITAL ABNORMALITIES AND ADVERSE OUTCOMES

Drugs can have harmful effects on the fetus at any time during pregnancy. It is important to bear this in mind when prescribing for a woman of childbearing age. During the first trimester AEDs may produce congenital malformations and the period of greatest risk is from the third to the eleventh week of pregnancy. During the second and third trimester AEDs may affect the growth and functional development of the fetus or have toxic effects on fetal tissues, and drugs given shortly before term or during labor may have adverse effects on labor or on the neonate after delivery.[24]

Major malformations are defined as defects of medical, surgical or cosmetic importance. This type of anomaly, which will seriously affect a child's life, occurs in 2 to 3 percent of all live born children. The risk of malformation is about twice that for the general population. Birth defects occur in 4% to 6% of infants born to women with epilepsy.[25] For women with epilepsy on one AED, the incidence is estimated to be 4 to 8 percent and possibly greater for women on

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polytherapy. Types of major malformations occurring most often in children of women with epilepsy are orofacial clefts, cardiac abnormalities and neural tube defects.[26] Ultrasound between 16 and 18 weeks gestation to check for abnormalities with an accuracy rate of over 95% is recommended during the antenatal care visits. Minor Anomalies such as hypertelorism, epicanthal folds, shallow philtrum, distal digital hypoplasia, and simian creases are often present as a familial trait and do not cause any serious problems and are primarily of cosmetic concern. The incidence of minor physical defects in infants born to women with epilepsy is approximately 15 percent.[27]

A greater incidence of mental retardation and/or microcephaly has been reported, but these studies have been inconsistent and have not always been controlled for other possible contributing factors such as inherent genetics, and the effects of maternal seizures or AEDs in utero.[28] However, developmental delays may be significant in terms of risk to infants of women with epilepsy. Factors other than the maternal epilepsy that are thought to be important are IQ scores in the mother and AED polypharmacy particularly exposure to phenobarbital in utero.[29] The development of language skills in particular tends to be slower. This is reported in 2% to 6% of births and sometimes is not permanently impaired; however, catch up varies.[30] A differential effect of individual AEDs has been identified in retrospective and prospective studies of young and older children who were exposed to AEDs *in utero*. Phenobarbital exposure resulted in a 7-point reduction in verbal IQ in adult men who had been exposed to phenobarbital during gestation, compared with controls whose mothers did not take AEDs during pregnancy.[31]

Long-term studies on neurodevelopment show higher rates of abnormal EEG findings, higher rates of developmentally delayed children, and lower intelligence quotient (IQ) scores.[32]

These babies also have a slightly higher risk of developing seizures as they get older.[33] Developmental delays are possible as well.[34]

There is no increased risk of early fetal death following spontaneous abortion within the first 20 weeks post-conception in women with epilepsy. Whereas, late fetal loss shows as much as twofold increased in incidence in women with epilepsy.[35]

Distinctive malformations and syndromes have been ascribed to phenytoin, phenobarbital, primidone, valproate, carbamazepine, and trimethadione. Specific increases in congenital abnormalities observed in infants born to mothers with epilepsy include a 4-fold increase in cleft lip and palate and a 3- to 4-fold increase in cardiac anomalies.[36] An increase in the rate of neural tube defects is also observed in the offspring of patients with epilepsy who are using valproic acid (1-2%) or carbamazepine (0.5%).[37] Folic acid supplementation (at a minimum dose of 0.4 mg daily) is especially important prior to conception and during pregnancy in women with epilepsy to lower the risk of neural tube defects in the offspring.[38]

Many experts believe that trimethadione is contraindicated in women with epilepsy who might become pregnant because it has been associated with a high incidence of fetal loss and congenital malformations.

Most of the literature suggests that first-trimester use of even a single AED is associated with a 2- to 5-fold increase in major malformations. Furthermore, multiple studies present evidence indicating an increase in fetal malformations with AED polytherapy. All commonly used AEDs have been associated with congenital malformations. Lamotrigine metabolism and clearance increases during pregnancy, and understanding the effect of pregnancy on lamotrigine concentrations is particularly important as this drug is being used increasingly in women who are considering pregnancy.[39] Some of the newer AEDs have not been used in large enough numbers to have meaningful data (Table 1).[40]

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MECHANISMS OF TERATOGENICITY

The mechanisms of teratogenicity of the AEDs have not been fully characterized. All AEDs have a similar central mechanism of action, a common pathway that is disrupted during embryogenesis may lead to the similarities in the syndromes described, and this may be why an additive effect is observed with polytherapy.[41] Phenobarbital, primidone, and phenytoin act as folate antagonists, certainly resulting in neural tube defects; thus, folate administration prior to conception has been recommended for prophylaxis. Recent studies in teratogenesis, particularly fetal hydantoin syndrome, point to a genetic predilection for the generation of epoxides. Holmes LB, These anomalies have been observed at an increased rate in children whose enzyme activity of epoxide hydrolase is one third less than the reference range. Anomalies have also been observed in children with low epoxide hydrolase activity who were exposed to carbamazepine.[42] Syndromes related to several of the AEDs, and to specific abnormalities observed in patients with seizure disorders, are not known to affect rates of chromosomal abnormalities.

Table 1. Teratogenicity and Breast Feeding advices associated with some of the Newer AEDs

Anti-epileptic Drug	Teratogenicity and Breast Feeding
Gabapentin	Present in milk-manufacturers advices avoid
Lamotrigine	Present in milk but limited data suggest no harmful effects on infants.
Levetiracetam	Present in milk-manufacturers advices avoid
	Toxicity in animal studies manufacturers advices avoid unless potential benefit outweighs risk
Oxcarbazine	Present in milk-manufacturers advices avoid
Pregabalin	Present in milk in animal studies-manufacturers advices avoid
Topiramate	Present in milk-manufacturers advices avoid
	Toxicity in animal studies manufacturers advices avoid unless potential benefit outweighs risk
Tiagabine Vigabatrin	Present in milk-manufacturers advices avoid
Zonisamide	Present in milk-manufacturers advices avoid. Toxicity and tertogenicity reported- manufacturers advices avoid unless potential benefit outweighs risk avoid; present in milk-manufacturers advices avoid breast feeding for 4 weeks after administration

NB. With careful treatment of these patients, more than 90% have an entirely uncomplicated and safe pregnancy. The side effects of antiepileptic drugs should not outweigh the benefits of treatment.

Hereditary epilepsy

The risk for babies of epileptic mothers to develop epilepsy is two folds of their control. About 2% of the children whose mothers have epilepsy will have epilepsy. However, a father with

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epilepsy does not seem to increase the risk.[43]

Infant mortality

Maternal epilepsy increase infant death after birth by two to three times. The rates are high right through the first year of life. The reason for the high mortality rate is unclear, but may be ascribed to high rate of birth defects.[43] In general, the fetus is protected from the physiologic effects of maternal seizures, but miscarriages can occur with prolonged seizures or status epilepticus

Hemorrhagic Disorder of the Newborn

Bleeding related to certain AEDs was once a major complication in newborn children of mothers with epilepsy, but it has been declining. This is a unique hemorrhagic disease of the neonate that occurs in the first 24 hours of life. Vitamin K prophylaxis is recommended in the last few weeks of pregnancy, starting at approximately week 36. The incidence of hemorrhagic disease in the newborn child has been reported to be increased in infants exposed to AEDs during pregnancy—in particular, AEDs that induce the Cytochrome P450 enzyme system. Cytochrome P450 enzyme-inducing AEDs, including phenobarbital, primidone, phenytoin, carbamazepine and, to a lesser extent, oxcarbazepine and topiramate, induce fetal microsomal enzymes, which degrade vitamin K. In addition, these drugs might cause competitive inhibition of the addition of calcium-binding γ-carboxyglutamic-acid residues to the precursors of clotting factors II, VII, IX and X. Bleeding in AED-exposed infants typically occurs early, and includes intra-abdominal, intracranial and intrathoracic locations. Maternal AEDs competitively inhibit vitamin K transport across the placenta and the infant has prolonged prothrombin and partial thromboplastin times. vitamin K supplementation at a dose of 10 mg/ each day during the last four weeks before delivery is recommended as a preventive measure.[44]

Low birth weight

Low birth weight in infants of mothers with epilepsy that is not related to prematurity was reported as twice as in the control.

Risk of Seizures in the Child

There is a higher risk for women with epilepsy to have children with the condition than for men with epilepsy. Seizure type and age of onset also affect incidence of epilepsy in the child. It is encouraging to recognize that even for patients in the highest risk groups, the risk that an offspring will develop epilepsy is less than 10 percent.[45]

MANAGEMENT

Women with epilepsy should follow the traditional rules for having a healthy pregnancy. Preconceptional counseling and coordination of care among all members of the health care team is the key to treating women with epilepsy of reproductive age.

Preconceptual management of women with epilepsy

Regarding the preconceptual management of women with epilepsy the following measures may be very useful;

- Attempt to decrease pharmacotherapy to monotherapy. Patients are advised to switch to a single AED prior to conception and taper to the lowest possible dose, because exposure to multiple antiepileptic drugs carries more teratogenic effects. Although this has not been studied in a prospective randomized clinical trial, using AED as monotherapy might offer lower fetal/embryonic risk.
- Taper dosages of AEDs to the lowest possible dose.

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- In women who have not had a seizure for 2-5 years, attempt complete withdrawal of pharmacotherapy prior to conception.
- Establish the level of total and free AEDs necessary for achieving good clinical control. Evidence indicates that high peak plasma levels of valproic acid may be more teratogenic, this drug should be dosed at 3-4 times per day rather than the standard twice-per-day dosing.
- Consider preconceptual genetic counseling.
- Supplement the diet with folate at 4 mg/d. Supplemental folate has been shown to decrease neural tube defects in patients without epilepsy and decrease other congenital anomalies in women with epilepsy. Thus, all women on AEDs, and particularly those using either valproic acid or carbamazepine, should be advised to take supplemental folate prior to conception.

However, patients with epilepsy should be counseled that they are still at a greater risk (ie, 4-6% vs 2-3%) for fetal anomalies than the general population. Because of the increased risk, a level II fetal survey should be performed at 19-20 weeks' gestation, with careful attention to the face, central nervous system, and heart. A fetal echocardiogram should also be considered to diagnose potential cardiac anomalies.

Management of women with epilepsy during pregnancy

Maternal serum alpha-fetoprotein (MSAFP) screening test to check for neural tube defects is particularly recommended in the setting of a family history of neural tube defects or with the use of valproic acid or carbamazepine.[46] Although the sensitivity of amniocentesis is higher than either MSAFP screening tests or ultrasonography for detecting neural tube defects its routine use is controversial.

Antiepileptic drugs may increase vitamin K metabolism and inhibition its placental transport, lead to increased risk of spontaneous hemorrhage in newborns. Upon delivery, clotting studies can be performed on the cord blood, and routine injection of vitamin K at birth effectively counteracts any AEDs associated risk of neonatal hemorrhage. However, a study of 204 neonates born to mothers taking AEDs who did not received vitamin K supplementation showed no evidence of coagulopathy.[43] If the cord blood is deficient in clotting factors, fresh frozen plasma may be required to protect the newborn.

Management of a pregnant patient in status epilepticus

Status epilepticus carries a high mortality rate for mother and fetus, and generalized seizures occurring during labor can result in fetal bradycardia. Rarely, a patient has intractable seizures upon labor and delivery. When the seizures last longer than 30 minutes with a continuous seizure or a lack of full recovery between seizures, the patient is considered to be in status epilepticus. Preeclampsia and eclampsia have to be excluded.

The protocol for managing status epilepticus is similar to the management of any seizure, ie, using benzodiazepines, phenytoin, and, rarely, phenobarbital. During this situation, the fetus must be monitored. Establish an airway and attempt intrauterine resuscitation. If the seizure is not treated easily and the fetal testing results is not reassuring for longer than 10 minutes, a neuromuscular blocking agent can be administered and emergent cesarean delivery can be performed.[18]

- Establish the ABCs, and check vital signs, including oxygenation.
- Assess the fetal heart rate or fetal status.
- Rule out eclampsia.

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- Administer a bolus of lorazepam (0.1 mg/kg, i.e., 5-10 mg) at no faster than 2 mg/min.
- Load phenytoin (20 mg/kg, i.e., 1-2 g) at no faster than 50 mg/min, with cardiac monitoring.
- If this is not successful, load phenobarbital (20 mg/kg, i.e., 1-2 g) at no faster than 100 mg/min.
- Check laboratory findings, including electrolytes, AED levels, glucose, and toxicology screen.
- If fetal testing results are non-reassuring, move to emergent delivery.

Management of women with epilepsy during labor and delivery

Careful management of pregnant women with epilepsy who are being treated with AEDs is important, as seizure frequency can change during pregnancy, and both seizure activity and AED drug treatment might have consequences for the developing fetus, including increased rates of stillbirth, teratogenesis and cognitive delay. Labor management should be based on routine standards of care and should include preparation and close monitoring. However, due to the fact that trauma and hypoxia from a seizure can put both the mother and fetus at risk, all care providers, including nurses, anesthesiologists, and pediatricians, that the patient has epilepsy, should be informed during labor and delivery that the patient has epilepsy and treatment of seizures should be discussed with the team caring for the patient. Manage seizures acutely with intravenous benzodiazepines (1-2 mg of diazepam), then load phenytoin (1 g loaded over 1 h).[18]

Antiepileptic drugs levels should be checked upon admission. If the serum drug level is low, patients may be administered extra doses or may be switched over to intravenous benzodiazepines or phenytoin. Consider seizure prophylaxis with intravenous benzodiazepines or phenytoin. Manage seizures acutely with intravenous benzodiazepines (1-2 mg of diazepam), then load phenytoin (1 g loaded over 1 h).

Reports of increased risk of spontaneous hemorrhage in newborns suggest that the inhibition of vitamin K–dependent clotting factors (ie, II, VII, IX, X) secondary to increased vitamin K metabolism and the inhibition of placental transport of vitamin K results from AED use. Historically, most patients on AEDs received oral vitamin K supplementation at the end of pregnancy. However, a study of 204 neonates born to mothers taking AEDs who did not received vitamin K supplementation showed no evidence of coagulopathy.[44] Upon delivery, clotting studies can be performed on the cord blood, and vitamin K can be administered to the infant. If the cord blood is deficient in clotting factors, fresh frozen plasma may be required to protect the newborn.

RECOMMENDATIONS FOR MANAGEMENT OF EPILEPSY IN PREGNANCY

Issues must be discussed with all epileptic women with childbearing potential. Simplification of regimen and optimization of dose before pregnancy is essential if AEDs are really needed. Key guideline recommendations for managing epilepsy during pregnancy include:

- Consideration must be given to whether AEDs are needed.
- If possible, women with epilepsy should avoid taking multiple AEDs to reduce the risk of birth defects.
- An epileptic mother should be given the right medication in the right dose. Generally AEDs that are effective and well tolerated should not be changed. Initial selection of drugs with the least teratogenicity, such ad carbamazepine, clobazam or possibly one of the newer AEDs, is recommended in women who wish to become pregnant.[47]

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- An epileptic mother should be enforced to a have good compliance.
- Breastfeeding is a viable option for epileptic mothers on AEDs. Caution and clinical monitoring should be exercised if the mother is using phenobarbital, primidone, ethosuximide or lamotrigine. AEDs enter the breast milk in inverse proportion to their protein binding. Sedating effects, such as the barbiturates, may cause sedation of the newborn.
- Epileptic pregnant women should have their blood tested and adjusted regularly to keep them seizures free. Pregnancy has been shown to lower the levels of AEDs in the blood, which may put women at risk of seizures.[48]
- They should be close to normal weight levels, and eat a sensible and balanced diet
- Smoking substantially increases the risk of premature contractions, labor, and delivery in women with epilepsy.
- There is little evidence to support or refute vitamin K supplements during pregnancy to reduce risk of perinatal hemorrhage.[44]
- Avoid use of valproate as evidence from numerous studies link the drug to major congenital abnormalities. These abnormalities include neural tube defects, facial clefts, and hypospadias.
- Valporic acid and carbamazepine should be avoided if there is a family history of or previous child with spina bifida. Phenytoin and phenobarbital should be used with caution because they can impair cognitive development in children and the latter may cause withdrawal symptoms after the first week postpartum.
- Use of as few AEDs as possible. There is increased cognitive impairment in children when mothers take multiple anticonvulsants during pregnancy.
- Women who have epilepsy and are considering pregnancy should be consider not doing so until they have been seizure-free for at least nine months prior to conception. This will give them an 84-92% chance of remaining seizure free during pregnancy.
- Folic acid supplementation is essential as in all pregnant women, it is even more so in women taking AEDs. At least 400 micrograms of folic acid a day, as supplementation has been shown to be "possibly effective" in preventing major birth defects.
- Epileptic mothers must be taught precautions when taking care of newborns or young children, such as changing and feeding the baby while sitting on a blanket on the floor and never bathing the baby alone.

Conclusion

Pregnancy in patients with seizure disorders can be complicated by a variety of maternal and fetal issues. Patients can experience higher rates of seizures and the fetus is likely to be at increased risk for congenital abnormalities and long-term outcomes such as lower IQs and higher rates of developmental delay. The teratogenicity effect of AEDs is reduced if treatment is limited to a single drug.

Epilepsy in a pregnant lady needs management by a team of care providers, including a perinatologist and a neurologist, and the mother should be counseled and given antenatal screening.

The common treatment strategy has been to use the appropriate AED for the woman's seizure disorder as monotherapy in the lowest effective dosage throughout pregnancy, the objective being to use AEDs in such a way that generalised tonic-clonic seizures are avoided but

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with minimized risks to the fetus, the newborn and the breast-fed infant. Valproic acid should be avoided if possible.

Issues that need to be addressed in further studies include better differentiation of which AEDs result in higher rates of major malformations, defining cognitive effects of in utero AED exposure. Breast feeding is generally safe. Larger scale studies are needed to better understand drug transfer in breast milk and metabolism in infants for all AEDs , and to establish better guidelines for breastfeeding.

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