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Treatment of Epilepsy in Pregnancy

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Abstract

Pregnant women with epilepsy constitute 0.5% of all pregnancies. Proper seizure control is the primary goal in treating women with epilepsy. The commonly used anticonvulsants are established human teratogens. Factors such as epilepsy, anticonvulsant-induced teratogenicity, patient's genetic predisposition and the severity of convulsive disorder may attribute to adverse pregnancy outcome for the children of women with epilepsy. Anticonvulsant interaction with folic acid and phytomenadione (vitamin K) metabolism may lead to an increased risk for neural tube defect and early neonatal bleeding. Psychological, hormonal and pharmacokinetic changes in pregnancy may escalate seizure activity.

Preconceptional counselling should include patient education to ensure a clear understanding of risks of uncontrolled seizures and possible teratogenicity of anticonvulsants. Genetic counselling should be performed if both parents have epilepsy or the disease is inherited. Seizure control should be achieved at least 6 months prior to conception and, if clinically possible, by the lowest effective dose of a single anticonvulsant according to the type of epilepsy. The new anticonvulsants are not recommended in pregnancy and require further research to prove their safety in humans.

Folic acid 5 mg/day should be administered 3 months before conception and during the first trimester to prevent folic acid deficiency-induced malformations. Antenatal management should include assessment of patients for anticonvulsant-associated birth defects through detailed ultrasound examination and levels of maternal serum α-fetoproteins. Therapeutic drug monitoring should be per-

formed monthly, or as clinically indicated. If phenobarbital, carbamazepine or phenytoin is administered, maternal phytomenadione supplementation should begin 4 weeks before the expected date of delivery.

In order to prevent convulsions during labour, proper seizure control should be achieved during the third trimester. Benzodiazepines or phenytoin are found to be effective for seizure cessation during labour and delivery. Phytomenadione should be administered immediately after birth to the newborn. The neonate should be assessed carefully for epilepsy and anticonvulsant-associated dysmorphology. Advising the patient on postpartum management regarding contraception and breast-feeding will help maximise the best possible outcome for the newborn and mother. With proper preconceptional, antenatal and postpartum management up to 95% of these pregnancies have been reported to have favourable outcomes.

Epilepsy, although not common among pregnant women, is the most common neurological disorder during gestation. Increased public awareness of the progress in diagnosis and management of epilepsy have enabled many women with epilepsy to bear children and manage careers.[1-2] Pregnant women with epilepsy constitute 0.5% of all pregnancies and medical professionals should be aware that with appropriate selection of treatment and prudent preconceptional, antenatal and postpartum management, up to 95% of these pregnancies have been reported to have favourable outcomes.[3] The evaluation of risk and safety of pregnancy in such women is complicated by a variety of factors. Women with epilepsy are at risk of menstrual abnormalities, reproductive endocrine disorders and reduced fertility.[4] Polycystic ovaries, hypo- or hypergonadotrophic hypogonadism are more common in women with epilepsy than in the general population. The investigators relate those abnormalities to the effect of seizures on the hypothalamic–pituitary-gonadal axis[5] and to a possible adverse effect of anticonvulsants.[6,7]

Even when not exposed *in utero* to medications, infants of mothers with epilepsy have higher rates of major and minor malformations[8,9] when compared with the general population. To add to the complexity, several commonly used anticonvulsants are established human teratogens. A large number of studies in humans and from animal investigations have shown a consistently increased risk for congenital malformation following anticonvulsant exposure *in utero*. Table I presents congenital malformations in humans caused by anticonvulsants for which there is consensus among scientists.

No agreement has been reached among experts about which of the commonly used anticonvulsants is safest to the unborn baby. Research indicates that the incidence of major and minor malformations is influenced by the number of anticonvulsant medications, the dosage of the drug, timing of use during gestation, pharmacokinetics and differences in metabolism.[8,10] Some investigators hypothesise that anticonvulsant-induced teratogenicity occurs in genetically predisposed individuals.[11] Other researchers have reported that epilepsy *per se*, the type and severity of the seizure disorder, also contributes to the dysmorphology.[12] Considering the complex interaction between genetic and environmental factors, it is difficult to attribute congenital abnormalities in children of mothers with epilepsy to any single factor,[13] especially because of the lack of large enough studies with sufficient power to control for such determinants.

1. Mechanisms and Clinical Implications of Teratogenicity

Several mechanisms have been proposed for the teratogenic effects of anticonvulsants. Some anticonvulsive medications (e.g. phenytoin) form intermediate oxide metabolites which are known to be embryotoxic. Free active oxide radicals have been shown to bind to proteins and nucleic acids

Table I. Congenital malformations in humans caused by anticonvulsants

Structural and functional defects	Phenytoin	Valproic acid (sodium valproate)	Carbamazepine	Phenobarbital
Congenital heart defects	+	+	–	+
Cleft lip and/or palate	+	+	–	+
Neural tube defect	–	+	+	–
Genitourinary defects	+	+	+	+
Cognitive impairment	+	+	±	±
Minor anomalies	+	+	+	+

± denotes inconclusive evidence; + = defect present; – = defect absent.

and may interfere with DNA and RNA synthesis. Critical amounts of free radicals may increase the risk for perinatal death, intrauterine growth retardation and malformations.[14]

Scavenging enzymes capable of conjugating these free radicals to inactive substances, may prevent fetal damage, and variabilities in such enzymes may explain variable fetal outcome. Unstable intermediates can also be metabolised to nonreactive hydrodiones by epoxide hydrolase. It has been proposed that fetuses with low levels of free radical–scavenging enzymes and low activity of epoxide hydrolase are at increased risk of developing malformations associated with phenytoin. Polytherapy may lead to excessive amount of unstable epoxides, such as arene oxides, and inhibit epoxide metabolism especially in fetuses with a genetic defect in fetal epoxide hydrolase activity.[15]

Evidence for increased risk of major malformations with increasing numbers of anticonvulsants come from several epidemiological studies. Lindhout et al.[16] reported a 5% risk for birth defects in children of women with epilepsy who took 2 drugs concomitantly, 10% in those who took 3 drugs and more than 20% when 4 drugs were used. When the seizures were controlled with only 1 anticonvulsant, the malformation risk was only 3% (*vs* 2% as in untreated women with epilepsy or in the general population).

The occurrence of specific malformations depends on timing of exposure during embryogenesis.[10,17] Neural tube defects (NTDs) occur before closure of the neural tube between days 21 and 28 after the first day of the last menstrual period (LMP). Cleft lip occurs with exposure before day 35 and cleft palate before day 70, whereas congenital heart defects occur with exposure before day 42 post LMP.[18] Exposure after the first trimester should not affect rates of dysmorphology, except for the toxic effects on the brain, which develops throughout pregnancy.[19] The most commonly observed major malformations are heart defects, orofacial clefting, genitourinary malformations and NTDs.[13] Minor anomalies, which were described as a part of the fetal hydantoin syndrome,[20] were later hypothesised to be associated with maternal epilepsy and not necessarily with the anticonvulsants.[9,21,22] We have recently detected different patterns of minor anomalies caused by phenytoin, carbamazepine and untreated epilepsy.[9]

Because the vast majority of NTDs can be ruled out by maternal or amniotic fluid α-fetoproteins combined with ultrasound, these should be routinely performed in women taking carbamazepine or valproic acid (sodium valproate).

At the present time some practising neurologists prefer carbamazepine as the drug of choice in pregnancy.[18] Carbamazepine has a risk of 1% for NTD,[23] compared with 2% for valproic acid.[24] It does not cause acne, hirsutism or face coarsening as does phenytoin. While the fetal hydantoin syndrome has been consistently associated with cognitive damage to some children,[20] studies with carbamazepine do not suggest similar damage,[25] although the literature is not consistent[26,27] and further studies at preschool and school age are needed.

Koch et al.[28] suggested that valproic acid-exposed children had higher rates of neurological

dysfunction. Valproic acid serum concentrations at birth correlated with the degree of neonatal hyperexcitability and with the degree of dysfunction when the children were re-examined at the age of 6 years.[28] In a recent consensus opinion it was suggested that the anticonvulsive medication most effective for the type of epilepsy and seizure control for a given patient should be used.[18] Women in need of polytherapy are likely to experience more severe forms of epilepsy and drug-drug interaction, thus further increasing the risk for adverse pregnancy outcomes.[10]

Another mechanism which has been implicated in anticonvulsant-mediated teratogenicity is folate deficiency.[10] Up to 90% reduction in folate serum levels was reported in patients treated with phenytoin, carbamazepine and barbiturates. Conversely, valproic acid did not reduce folate levels directly, but by interfering with its metabolism.[29-30] Folate supplementation was found to be effective in preventing several malformations, but, in particular, NTDs. The Medical Research Council study[31] reported a 70% reduction of NTD recurrence among pregnant women who were supplemented with folic acid 4mg before conception and during gestation. The current recommendations call for folic acid 5 mg/day in women being treated with valproic acid or carbamazepine.[2,32] Presently, however, there are no data to document the efficacy of this regimen in women with epilepsy, but the potential benefit of such an approach outweighs the theoretical risk of high levels of folate.[33] Cyanocobalamin (vitamin B_{12}) levels should be assessed before folic acid supplementation in an attempt to avoid neurological symptoms of cyanocobalamin deficiency.[34]

The contribution of genetic and seizure effects on fetal developments with respect to congenital malformation is not well defined. A control group with a large enough sample size of unmedicated women with epilepsy has not been assessed by any research group. Even if collected, such a control group may represent less severe forms of epilepsy with a low frequency of seizures.

The effect of seizure activity during pregnancy on fetal well-being has been investigated by several groups.[35] Isolated seizures of short duration are generally believed to not have an adverse effect on the fetus. In contrast, spontaneous abortions, injury to the mother and fetus, fetal hypoxia, bradycardia and antenatal death have been reported[3,36,37] with repeated tonic-clonic, complex partial seizures and status epilepticus. There is ample evidence that physiological changes during pregnancy may affect the duration and frequency of seizures. Seizure rates have been reported to increase in 17 to 37% of women with epilepsy.[2,36] When seizures recur in a well controlled woman during pregnancy, most often it takes place during the first and second trimesters.[33]

Poor patient compliance, sleep disturbances, nausea, vomiting and decreased levels of free (unbound) drugs are the main risk factors believed to decrease seizure control.[18,38]

Increases in estrogen levels during pregnancy may reduce seizure threshold levels.[39] Progesterone reduces intestinal motility thus interfering with mucous secretion, gastric pH and may affect drug absorption.[38] Changes in seizure frequency during pregnancy may also stem from fluid and sodium retention, hyperventilation, and emotional and psychological problems.[40] A potential problem in the management of seizures may also arise from altered pharmacokinetics of anticonvulsants associated with pregnancy.

2. Pregnancy-Induced Pharmacokinetic Changes of Anticonvulsants

The plasma concentration of anticonvulsant drugs tends to fall during pregnancy as a result of a 50% expansion in plasma volume, decrease in protein binding,[41] increased clearance rate and a tendency towards decreasing patient compliance because of fears of teratogenicity. On the other hand, bound and free drug proportion changes (on steady-state conditions) may have only transitory clinical consequences due to the intrinsic ability of liver enzymes to metabolise the drug independently

of the extent to which the drug binds to the plasma proteins.[42]

As most anticonvulsant drugs are acidic or neutral, they are highly bound to serum albumin. During late pregnancy, albumin levels fall, with a corresponding decrease in the fraction of bound drug, which leads to a decrease in the total (unbound and protein bound) plasma concentration. The decrease in plasma protein binding leads to more free drug available for biotransformation and clearance. Although the free anticonvulsant levels fall much less than the total levels, they often do decline significantly during pregnancy.[18,43]

Monitoring the total plasma concentrations of anticonvulsants can, therefore, be misleading. In complex clinical cases therapeutic drug monitoring that can measure both protein-bound and unbound drug concentrations can be helpful. The measurement of free drug concentrations of highly bound drugs should be considered in cases where seizure control is not achieved. It should be remembered that the appropriate free drug concentration is crucial for anticonvulsive control, as it is the free drug that reaches the brain. The increase in glomerular filtration rate[44] (GFR) and renal plasma flow[45] may theoretically enhance the clearance rate of renally excreted drugs, such as gabapentin and vigabatrin. However, there are presently no studies available regarding the pharmacokinetics of these agents during human pregnancy.

2.1 Carbamazepine

Carbamazepine has a relatively slow absorption, with 70 to 80% of protein binding to albumin. The main elimination route is by hepatic metabolism, and there may be a decrease in serum concentrations during the first months of therapy as a consequence of auto-induction of metabolism. Dose intervals and sample time are critical in interpreting serum concentrations. Large peak-trough fluctuations can be minimised by using a controlled-release formulation.[46] The concentrations of controlled-release carbamazepine tend to be lower in pregnant when compared to nonpregnant women. As the bioavailability may be lower than with conventional carbamazepine, higher doses may be required when using controlled-release medications.[47]

The concentration of the active metabolite (carbamazepine-10-11-epoxide) was reported to increase during pregnancy, possibly as a result of the increased carbamazepine metabolism and impaired conversion of carbamazepine-10-11-epoxide to carbamazepine-10-11 *trans*-diol. This increase is of potential importance as the metabolite (10-11-epoxide) is believed to have comparable pharmacological activity to the parent drug.[48]

2.2 Phenytoin

Phenytoin follows nonlinear pharmacokinetics and has a narrow therapeutic window.[49] It is highly bound to protein (90 to 93%)[50,51] and cleared mainly by saturable hepatic metabolism. A substantial increase in 8-hydroxylation during pregnancy may be responsible, at least partially, for its increased clearance rate and consequently decreased serum concentrations.[52] Generally, a fall in total serum phenytoin concentrations may cause a lack of seizure control and may require increases in dosage. However, as indicated above (in section 2) , the total concentration by itself may not indicate a fall in free drug concentrations. The decrease in the protein binding of phenytoin may be an important mechanism for decreasing total drug concentrations in pregnancy as it is the free drug that is available for the enhanced metabolism.

2.3 Valproic Acid (Sodium Valproate)

Valproic acid is rapidly absorbed and highly protein bound to plasma albumin (88 to 92%).[53] The interpretation of its pharmacokinetics is limited by large fluctuations in the concentration-time profile, wide therapeutic index and concentration-dependent protein binding.[54,55] Analysis of unbound valproic acid is not routine and similarly there is no established therapeutic range. Dose adjustments during pregnancy are best made by clinical observation in combination with therapeutic drug monitoring. Divided doses are preferred to

avoid high peaks in serum concentrations of valproic acid.[18]

2.4 Phenobarbital

Phenobarbital has been less frequently prescribed during the last few years because of its tendency to produce sedation and impaired cognitive function. It has a high oral bioavailability (90%) and is only 50% protein–bound. Similar to phenytoin and carbamazepine, it induces hepatic microsomal oxidative enzymes and may interact with the therapeutic efficacy of other drugs.

Neonates exposed prenatally to phenobarbital should be monitored for withdrawal symptoms for 2 to 6 weeks. Such monitoring should start at day 7 of life because of the long elimination half-life (100 hours) of phenobarbital.

2.5 New Anticonvulsants

The new anticonvulsants tend to have low levels of protein binding (e.g. topiramate, felbamate, oxcarbazepine) or do not bind to protein (e.g. gabapentin, vigabatrin). They are eliminated from the body through renal clearance. Vigabatrin and gabapentin have no effect on the cytochrome P450 enzyme system, while gabapentin, lamotrigine and vigabatrin have no antifolate effects. The new anticonvulsants also have no arene oxide metabolites and if given in monotherapy may be considered for use for women with epilepsy, but there is little information regarding their pharmacokinetics and safety during pregnancy.

Animal studies have been extremely beneficial in understanding the mechanisms of adverse effects and teratogenicity of new anticonvulsants. They are very informative in testing hypotheses and assessing nutrition and environmental factors, which may interfere with or modify normal embryonic or fetal development. Although animal studies help to clarify pharmacokinetic changes in pregnancy and to define the risk factors associated with teratogenicity,[56] they may be imperfect predictors of human teratogenicity. Animals may exhibit increased sensitivity in response to much higher doses medication than in human exposure (tiagabine), or show species-specific effects, effects not observed in humans (topiramate).[57] However, recent reports regarding animal reproductive toxicology of new anticonvulsants appear to be promising. Although results of animal studies regarding teratogenic effects of the new anticonvulsants are encouraging, it is too early conclude whether such data will apply to humans.

The Lamotrigine Pregnancy Registry report[58] (September 1, 1992 through March 31, 1998) contains a description of all prenatal exposure to lamotrigine voluntarily and prospectively reported to the registry. In prospective reports, there were 0 (confidence interval [CI], 0 to 12.6) birth defects in 34 pregnancies associated with first trimester exposure to lamotrigine monotherapy. However, there were birth defects in 5.6% (n = 6), [95%CI, 2.3 to 12.3) of 107 pregnancies consisting of patients treated with either lamotrigine only, or lamotrigine and other drugs. Outcomes include 4 live born infants with birth defects (1 infant had 1 extra digit on 1 hand [mother took carbamazepine prior and throughout gestation], 1 infant had bilateral talipes, 1 infant had skin tags on the left ear and no opening to the ear canal on the right ear [mother took gabapentin prior to and throughout pregnancy], 1 infant had cardiac murmur and patent foramen ovale requiring banding around the pulmonary artery; baby died at 3 months following corrective surgery) and 2 induced abortions involving birth defects (outcomes included NTD associated with severe cetral nervous system and multiple organ abnormalities [n = 2]). In prospective reports of all trimesters of exposure combined, there were no birth defects in 37 outcomes. The registry findings of 5.6% of birth defects associated with monotherapy and polytherapy are not higher when compared with that expected in pregnant women with epilepsy.[8,9] There was no consistent pattern of malformations among defects reported. The Lamotrigine Pregnancy Registry Advisory Committee concluded that the number of exposed pregnancies outcomes represent a sample of insufficient size for reaching definitive conclusions regarding safety of lamotrigine in pregnancy.

2.6 Effect of Anticonvulsants on Phytomenadione (Vitamin K)

The association between maternal anticonvulsant therapy and neonatal haemorrhage was reported 40 years ago[59] and supported by a number of subsequent studies and reports.[60] These haemorrhages, which typically occur during the first 24 hours after birth (in contrast with classic neonatal bleeding which occurs on day 2 or 3 after delivery),[61] may be severe, involving the skin, brain and pleural and peritoneal cavities.

The mechanism and origin of these haemorrhages is not fully understood, but phytomenadione deficiency was observed in neonates exposed *in utero* to enzyme-inducing anticonvulsants such as carbamazepine, phenytoin, phenobarbital and primidone. These medications readily cross the placenta and induce liver enzymatic pathways resulting in increased degradation of phytomenadione and produce proteins that are induced by phytomenadione absence (PIVKA). These proteins are present when phytomenadione is absent in neonates exposed *in utero* to anticonvulsants. The decarboxylated form of prothrombin-PIVKA II, is the most sensitive marker for phytomenadione deficiency[62] and was proven informative in studies[62-65] of neonatal phytomenadione levels. Although phytomenadione does not easily cross the placenta from the maternal to the fetal circulation, prenatal supplementation of phytomenadione results in valuable effects in preventing neonatal bleeding.[66]

The consensus guidelines[18] regarding women receiving enzyme-inducing anticonvulsants call for antenatal maternal phytomenadione supplementation at 20 mg/day orally throughout the last 4 weeks of gestation and phytomenadione 1mg parenterally to the neonate immediately after delivery. If PIVKA is found in cord blood specimens, fresh frozen plasma should be given at a dose of 20 ml/kg over a period of 1 to 2 hours.[18] While some experts still debate the value of maternal antenatal supplementation during the last month of pregnancy, general agreement has been reached regarding the necessity of parenteral neonatal prophylaxis.[2]

3. Management Considerations

3.1 Preconceptional Counselling

Women should be counselled about the potential risk of increased seizure activity in pregnancy, to ensure that they do not avoid taking their medication. This is important since poor compliance, resulting in increased seizure activity, has tangible risks.

Preconceptional counselling should optimally begin at least 3 months before conception to allow adequate supplementation of folic acid. Adequate patient education regarding the increased incidence of major malformations[67] and possible adverse effects of anticonvulsant drugs to the fetal CNS[25,68] should be provided.

Genetic counselling should be offered if both partners have epilepsy or the epileptic disorder is inherited. Gradual drug discontinuation (over at least 3 months) should be considered if the patient has been seizure-free for 2 or more years. A woman with epilepsy who is planning a pregnancy should be encouraged to quit smoking, maintain sufficient nutritional intake and attain adequate sleep.[18]

If treatment with anticonvulsant medications cannot be avoided, proper seizure control should be reached by the lowest effective dose of a single anticonvulsant which best controls seizures in the individual patient. Alternatively, pregnancy should be delayed until desired seizure control is reached. It should be remembered that polytherapy and/or higher daily doses are associated with higher rates of congenital malformations.

If valproic acid is indicated, divided doses are preferred to avoid high peaks of valproic acid plasma concentrations.[18,69] Combination of valproic acid, carbamazepine and phenobarbital has been reported to be more teratogenic than other combinations.[33]

Folic acid supplementation at 5 mg/day, should start 3 months before conception until the end of the first trimester. If possible, serum folate levels should be monitored to confirm sufficient supplementation.

3.2 Antenatal Management

More than 50% of all pregnancies are unplanned[70] and if the pregnancy is confirmed while the woman is seizure free, there is no proven benefit in changing the patient's drug because the morphological teratogenic effects will be irreversible by 10 weeks of gestation.[18] The patient should be advised regarding appropriate prenatal diagnosis for anticonvulsant-associated abnormalities. For example, targeted fetal ultrasound examination at 18 weeks can diagnose open NTD in up to 95% of fetuses,[71,72] as can be other visualised anomalies.[73]

Early transvaginal ultrasonography at 11 to 13 weeks to assess for NTD is possible.[33] Detailed sonographic imaging of the fetal heart at 18 to 20 weeks followed by fetal echocardiography can identify up to 85% of cardiac defects. Imaging of the fetal face for cleft lip at 18 to 20 weeks may be performed, but the sensitivity of this assessment has yet to be established.[33]

Amniocentesis with amniotic fluid α-fetoprotein and acetylcholinesterase may support suspicious anatomy or blood serum tests.

Epoxide hydrolase activity in amniocytes has been suggested to identify fetuses at risk for phenytoin-mediated anomalies. However, this test is not yet available for routine clinical use. Phytomenadione supplementation of the mother is recommended, as detailed above (see section 2.6). Nausea and vomiting of pregnancy may increase the risk of seizures. Hence, it is imperative to treat epileptic women effectively. The most widely studied drug to be proven effective is the combination of doxylamine and vitamin B_6.[74] Other proven treatments are vitamin B_6 by itself, antihistamines and acupressure.[75]

Optimally, therapeutic drug monitoring should be performed every 1 to 2 months, or more frequently if seizure control is not achieved.

3.3 Labour, Delivery and Birth

Tonic-clonic seizures occur during labour or after delivery in 1 to 2% of women with epilepsy.[18] Monitoring plasma anticonvulsant concentrations during the third trimester, and regular administration of medication(s) are essential to prevent seizures due to inappropriately low serum concentrations.[3]

Convulsive seizures at the time of labour and delivery are commonly treated with intravenous administration of benzodiazepines or phenytoin. Intravenous administration of phenytoin should be given with cardiac monitoring to detect possible dysrhythmias.[71]

Emergency cesarean section is often performed when repeated tonic-clonic, psychomotor or absence seizures, or status epilepticus occur.[37]

Obstetric intervention in the form of induction of labour, mechanical rupture of membranes, forceps delivery and cesarean section are more common among women with epilepsy, as are obstetric complications, including vaginal bleeding, anaemia and preeclampsia.[3]

3.4 Management During Puerperium

Phytomenadione should be administered immediately after birth to the newborn. The neonate should be examined carefully for anticonvulsant- and epilepsy-associated dysmorphology. If the neonate was exposed to phenobarbital or primidone, observation for withdrawal symptoms should be performed during the first 7 months of life.

Maternal anticonvulsant drug concentrations should be carefully maintained with appropriate dose changes, bearing in mind that a decreased clearance rate postnatally may result in toxicity. The patient should be counselled regarding postpartum contraception. The use of oral contraceptive agents is not contraindicated in women with epilepsy.[59] For patients treated with hepatic enzyme-induced anticonvulsants a higher dose (estrogen 50μg) combination oral contraceptive pill will be needed to compensate for the higher rate of clearance of the hormone.

The issues of breast-feeding should also be discussed with the mother as most women with epilepsy can breast-feed. Phenytoin and valproic acid are highly protein bound and, therefore, only low levels of these drugs are present in breast milk. Carbamazepine and phenobarbital are present in high concentrations in breast milk. Because of the

sedative effect of phenobarbital, breast feeding is not recommended. When the mother is taking phenobarbital and breast-feeding, the infant must be monitored for the risk of lethargy and poor suck.

4. Summary

Proper seizure control is the primary goal in treating women with epilepsy. Patients should understand the risks associated with uncontrolled seizures as well as the teratogenicity of the anticonvulsive medication in question. If anticonvulsants cannot be avoided, the most appropriate first-line drug for the seizure type should be used at the lowest effective dose. Judicious preconceptional, antenatal and postpartum management lead to a favourable maternal and neonatal outcome in the vast majority of patients.

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