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Epilepsy and Antiepileptic Medications in Pregnancy

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One in two hundred pregnant women is epileptic. Many studies have established that the effects of epilepsy and antiepileptic drug treatments increase the risk of congenital malformations in the fetus. When examining the decision to administer antiepileptic drugs during pregnancy, the physician must weigh the risks of maternal seizures vs. the risk of teratogenic effects. This third issue of RISK//NEWSLETTER will focus on the possible teratogenic effects of many popular antiepileptic medications.

EPILEPSY

Epilepsy in general has been associated with an increased rate of malformations in offspring. There are three major concerns for women who have epilepsy: (1) how maternal epilepsy will affect the health of both the mother and the fetus; (2) the possible risk for the fetus to have a seizure disorder; and (3) the increased risk for congenital malformations as a result of teratogenicity from antiepileptic drug treatments. Because of the possible interactions among these factors, it is difficult to determine if the increased frequency of malformations is a result of maternal epilepsy, treatment, or a combination of the two.

Studies have shown that there definitely is an increased frequency of fetal malformations in offspring of women who have epileptic attacks during pregnancy (Kilpatrick, 1991). Approximately 1/3rd of epileptic women experience an increase in frequency of seizures during pregnancy. It is possible that this is due to noncompliance on the part of the mother because of fear of the teratogenic effects of antiepileptic medications. In any case, epileptic attacks and convulsions cause a risk of maternal and fetal hypoxia and acidosis, as well as increasing the fetal heart rate. During labor and delivery there is also the risk of preeclampsia and premature labor in the epileptic mother (Yerby, 1991 and Cleland, 1991).

ANTIEPILEPTIC MEDICATIONS:

VALPROIC ACID (VPA)

In animals, use of valproic acid (VPA) during pregnancy has been associated with dose-related teratogenic effects. In hamsters, doses 5X the normal human dose was associated with an increase in neural tube defects. At various doses, mice and rats showed dose-dependent cardiac, skeletal, urinary tract and behavioral defects. Cleft palate and renal defects were also common. Monkeys exposed to up to 15X the normal human dose of VPA during organogenesis showed an increase in skeletal and limb

malformations as well as an increased frequency of low birth weight. At 30X the human dose, VPA acid administered to the mother was embryolethal (Teris/Reprotox).

In humans, VPA has been associated with an increased frequency of congenital malformations (Kilpatrick, 1991). VPA use during gestation has been associated with an increase risk of spina bifida. Several human studies have suggested that use of VPA during pregnancy increases the risk of neural tube defects (NTD) 20-40X, to approximately 1-2%, as compared to the general population risk of 0.05%; this increased risk is comparable to that of a woman who has a previous child with a NTD. In utero exposure to VPA has also been associated with an increased risk of radial limb reduction defects and hypospadias in male fetuses (Sharony, 1991).

A fetal valproate syndrome has been defined. It is characterized by a distinct facial dysmorphism, which includes epicanthal folds, a flat nasal bridge with a broad base, anteverted nostrils, a shallow philtrum, and a thin upper lip with a thick lower lip. Growth retardation, limb and heart defects are also typical of the fetal valproate syndrome (Sharony, 1991). However, it is important to point out that several of these mothers were on multiple medications and it is difficult to assign causal effect as a result.

It is recommended that VPA be AVOIDED during pregnancy if possible, because of an increased risk of spina bifida and limb defects. If treatment is necessary, monotherapy is preferable, with dosages at the lowest possible level. Preconceptional folate supplements should be given and continued throughout the pregnancy to decrease the risk of NTD's. Ultrasound evaluation and MS-AFP testing are also recommended to screen for NTD's and limb defects in the fetus.

PHENOBARBITAL

In animal studies using doses of phenobarbital 9-38X the human therapeutic level there was a dose-dependent increased frequency of malformations, including cleft palate, cardiovascular defects, and facial dysmorphism. Non-epileptic pregnant women exposed to phenobarbital during pregnancy did not show an increase in frequency of malformations above the expected level (Teris). However, epileptic women exposed to this drug during pregnancy showed an increase in malformations comparable to that found when other antiepileptic drugs were used in monotherapy; this suggests that the teratogenic effects maybe the result of the epilepsy and not phenobarbital (Teris/Reprotox).

In retrospective human studies on epileptic women exposed to phenobarbital during pregnancy, there were significant associations between drug exposures and cleft lip with or without palate. Exposure to phenobarbital was also associated with growth reduction, especially head circumference and postnatal weight gain, and delays in psychomotor development (Kaneko, 1991). Other associated malformations included congenital heart defects, such as VSD, ASD and PDA (Sharony, 1991).

Use of phenobarbital in late pregnancy has been associated with neonatal withdrawal effects. The deficiency of vitamin K, which this drug can also produce late in pregnancy, has led to the recommendation of vitamin K supplementation.

PHENYTOIN/HYDANTOIN

The Collaborative Perinatal Project found an association with regular use of phenytoin in early pregnancy and an increased frequency of malformations in offspring (Dansky, 1991). Use during pregnancy has also been associated with an increased frequency of cleft lip and palate as well as congenital heart disease, especially when used in polytherapy with phenobarbitone (Kilpatrick, 1991). It is possible that the teratogenic effects of this drug are the result of a decrease in fetal epoxide hydrolase, which is required to prevent toxicity; there are also indications that this decrease may be influenced by a genetic susceptibility (Sharony, 1991).

Hanson and Smith (1975) have characterized a fetal hydantoin syndrome which may severely affect up to 5-10% of infants exposed to phenytoin in utero; there is no doubt that the risk for birth defects in children exposed to phenytoin in utero is at least double the risk of the general population (Teris). An additional 30% are mildly affected, suggesting a genetic disposition to the effects of teratogenic exposures (Sharony, 1991), Cleland, 1991). Similar findings have been associated with animal exposures to phenytoin. The fetal hydantoin syndrome is characterized by hypertelorism, a flat and broad nasal bridge, epicanthal folds, microcephaly, digital/nail hypoplasia, and mental retardation (Cleland, 1991). IUGR and postnatal growth deficiency are also commonly seen (Sharony, 1991).

Finally, in utero exposure to phenytoin may decrease important vitamin K dependent clotting factors and increase the risk of fetal hemorrhage at delivery; for this reason, it is suggested that vitamin K be given to the mother a few days before delivery and to the neonate immediately after birth (Kilpatrick, 1991).

CARBAMAZEPINES

In animals given 5-100X the normal human dosage of carbamazepine during pregnancy, there was an associated increase in congenital defects, including CNS abnormalities. In human studies of carbamazepine use during gestation, an increased frequency of malformations was present in offspring, but this level was similar to the frequency seen in other antiepileptic therapy during pregnancy. Eighteen percent of women exposed to carbamazepine showed associated malformations (Reprotox, 1993).

In one study, use of carbamazepine during pregnancy was associated with a significantly smaller fetal head circumference at birth; within 5 years this was no longer a statistical significant difference, and IQs were within normal range (Teris, Kaneko, 1991). In a prospective study, there were also associations with low birth weight and decreased fetal growth, both prenatally and postnatally, in 6% of exposed infants. Twenty percent showed developmental delays, and 11% showed craniofacial dysmorphology. Congenital heart defects, nail hypoplasia and urogenital defects were also seen in some cases exposed to carbamazepines in utero (Jones, 1989). These findings were similar to the fetal hydantoin syndrome (Sharony, 1991). Case studies also suggest a possible risk of up to 1% for neural tube defects, but there are no epidemiological studies to support this (Teris, Rosa (1991), VanAllen (1988) (cited in Shepards). When carbamazepine is used in polytherapy, especially with Valproic acid, the risk of malformation is increased.

BENZODIAZEPINES (BZDs)

In humans, the use of benzodiazepines has been fairly well documented; approximately 1-3% of all pregnancies are exposed to benzodiazepines at some point. Use of benzodiazepines (BZDs) during the first trimester has been associated with a significant increased frequency of cleft lip and palate; this finding has not been consistently present.

Laegreid and colleagues (1990) described a fetal syndrome related to heavy use of BZDs during pregnancy. Excessive maternal exposure to BZDs was associated with facial dysmorphology similar to the fetal alcohol syndrome, impaired growth, CNS abnormalities, low birth weight, hypotonia, delayed motor development, transient neonatal withdrawal, and mental retardation. In a later case-controlled study, Laegreid (1992) showed significant associations between use of BZDs during early pregnancy and embryopathy and fetopathy, CNS malformations, cleft lip and palate and urinary tract malformations. Other studies failed to support Laegreid's association with a fetal syndrome, suggesting that perhaps chronic use at high doses is required to produce these effects. Use of BZDs late in pregnancy have also been associated with neonatal withdrawal symptoms and hypotonia (Laegreid, 1992).

Diazepam is the most studied BZD. This drug is known to freely cross the placenta and accumulate in the fetal circulation. There have been some associations between the use of diazepam during pregnancy and oral clefting, but no causal relationship has been firmly established.

SUMMARY

In summary, maternal epilepsy and the use of antiepileptic drugs during pregnancy has been associated with an increased frequency of fetal malformations. Overall, the risk for fetal malformations in offspring of epileptic women is approximately 4-6%, compared to the general population risk of 2-3% (Kaneko, (1991), Yerby, (1991)). The risk of perinatal mortality among epileptic mothers is approximately 2-4%, compared to the background level of less than 1% (Dansky, 1991). When seizures occur during pregnancy, the risk of stillbirth doubles, 5.1% compared to the general population risk of 2.4%. Epilepsy also increases the risk of fetal hypoxia (Kilpatrick, 1991).

Studies suggest that the risk of fetal malformations is increased with the use of antiepileptic medications (AEDs) over the already increased risk for untreated epileptic women, and that polytherapy increases the risk over monotherapy. There is a significant association between dose of AED and increased frequency and severity of malformations; however, as dose of AED is also related to severity of epilepsy in most cases a direct causal affect of higher dose and severity of malformation cannot be made (Kilpatrick (1991), and Cleland (1991)).

The risk for spontaneous abortion is increased in epileptic mothers who are exposed to AED treatment during pregnancy, perhaps as the result of the decreased levels of thyroid hormone normally responsible for maintaining the viability of the pregnancy (Kaneko, 1991). A combination of 12 prospective human studies reported that the risks of fetal malformation in epileptic women using AED was 11%, versus 5.7% for children of epileptic mothers who were not using AEDs during pregnancy (Kaneko, 1991). A compilation of 15 retrospective studies suggested that both risks may be lower- 7.8% for epileptic women who use AEDs during pregnancy and 3.4% for women who do not. In addition, 7-11% of children who are exposed to AEDs in utero show developmental defects, which may be due to a possible genetic predisposition or to environmental effects. Many of the fetal syndromes seen in association with AED use during pregnancy show similar features, suggesting that perhaps many of the teratogenic effects in infants of women exposed to AEDs during pregnancy are a result of the maternal epilepsy rather than the AED exposures; however, no causal relationship has been established.

The most common malformations in offspring of epileptic mothers are cardiovascular (1.8%), Skeletal (2.3%), Clefting (1.6-1.8%), gastrointestinal (0.9%), CNS (0.8%), and genitourinary (0.9%) (Kaneko, 1991).

Based on retrospective and prospective studies, the risk for cleft lip or palate after AED exposure is significantly increased to 1-1.9%, as compared to the general population risk of 0.2%; however this may be due to epilepsy rather than AED exposure (Kaneko, 1991). There is also a 2-8X increased risk for congenital heart defects (Kaneko, 1991). Low birth weight, reduced length, and a significant increase in the occurrence of microcephaly have also been seen with increased frequency in offspring of epileptic mothers. Limb defects, including radial ray reduction deficits, have been reported, as well as various facial dysmorphologies (Sharony, 1991). There is an increased risk of 1-2% for spina bifida when VPA is used during pregnancy; when carbamazepine is used in polytherapy it also has an increased risk of 0.5-1.0% for neural tube defects. Finally, there is a 2-7X increased risk of mental retardation in children exposed to AEDs in utero. Recent research also suggests that some AEDs may work on the developing brain and nervous system in the 2nd and 3rd trimesters to produce behavioral teratological effects. More research is required to confirm this finding.

Some sources recommend withdrawing antiepileptic medications if the woman has been seizure-free

for 2 years or if her epilepsy is mild with infrequent or partial seizures (Cleland, 1991). However, there is a difference in medical thought over withdrawal for the entire pregnancy vs. only the first trimester during when much of the teratogenicity occurs. Polytherapy i.e., has been associated with an increased frequency of minor anomalies and more severe teratogenic effects, when compared to monotherapy; for this reason, monotherapy is recommended whenever possible.

Preconceptual folate supplements continued throughout the pregnancy may help decrease the risk for neural tube defects. Also, vitamin K supplements should be given to the mother during the third trimester and immediately before/during labor and delivery in order to prevent fetal hemorrhage (Kilpatrick, 1991). Regular ultrasound can be used throughout the pregnancy to detect many of the malformations frequently seen in children of women with epilepsy, such as growth deficits, small head circumference, limb defects, clefting and neural tube defects (Sharony, 1991). Maternal serum alpha-fetoprotein (MS-AFP) testing is also an appropriate screening measure because it can detect 70-80% of all neural tube defects.

At birth, fetal withdrawal symptoms are common in infants exposed to AEDs in utero; especially those exposed to phenobarbital, primidone and phenytoin. The withdrawal symptoms have been known to last up to 6 months. Also, care should be taken with breastfeeding, as phenobarbital, diazepam and primidone are eliminated in breast milk for 5-7 days after maternal ingestion; the neonate may show extreme drowsiness and feeding problems if exposed to antiepileptic drugs postnatally (Kaneko, 1991).