Epilepsy and pregnancy

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MANAGEMENT of women with seizures during and immediately after pregnancy poses multiple potential problems for the neurologist and obstetrician. As demonstrated in several studies, about one quarter to one third of pregnant epileptic women will have an increased frequency of seizures during pregnancy; but with close monitoring of anticonvulsant blood levels and appropriate dosage adjustments most women will have no significant increase in seizure frequency.

With good prenatal care, obstetrical complications can be held to a minimum. Investigators have noted an increase in the frequency of fetal malformations in epileptic women and an even higher frequency if such women are taking anticonvulsants during pregnancy. Trimethadione is contraindicated during pregnancy; and women receiving valproic acid should be monitored for fetal neural tube defects, which occur at a frequency of 1% to 2%. Hemorrhagic disease of the newborn may be prevented by treating the mother with vitamin K before delivery and giving the neonate 1 mg vitamin K parenterally at delivery. In most circumstances, breast feeding is permissible. Because of enhanced metabolism, oral contraceptives have a higher failure rate in women taking anticonvulsants.

This review addresses various issues concerning epilepsy and pregnancy, with an emphasis on studies generated in the past 10 years. Previous reviews of these subjects include those of Montouris et al,[1] Philbert and Dam,[2] Dalessio,[3] and Robertson.[4] *Epilepsy, Pregnancy and the Child* edited by Janz et al is an invaluable source of information.[5]

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FERTILITY

Earlier in this century, it was relatively common for states to have legal prohibitions against epileptics either marrying or having children. Those laws have been repealed, with Missouri being the last in 1982.[6] Nevertheless, the marriage rate for epileptics is significantly lower than for other populations of comparable age. In a Canadian study, the overall marriage rate for female epileptics was 83% of the rate for nonepileptics; for males, the rate was only 59% of the expected rate. The difference was most marked for patients with seizure onset in the first decade. Of the married male and female patients, Dansky et al[7] found a normal fertility rate for the males but for females the overall fertility rate was only 69% of that expected, falling to 43% if seizure onset was in the first decade. Lindsay et al[8] also drew attention to the decreased marriage and fertility rates for both male and female epileptics; in addition they echoed Taylor's[9] finding of the relatively common lack of sexual interest in the epileptic male population.

SEIZURES AND PREGNANCY

A pregnant woman with a history of seizures or with the development of seizures is a relatively common obstetrical problem. In the National Collaborative Perinatal Project of 45,000 pregnant women, 2.1% had at least one noneclamptic seizure before or during pregnancy.[10] In a review of multiple series, approximately 12.8% of epileptic women reported onset of epilepsy during pregnancy; in the opinion of the reviewer, however, this occurrence was probably coincidental.[11]

A small number of women will have seizures only

during pregnancy ("gestational epilepsy"). Knight and Rhind[12] identified 14 women who had seizures only during 39 pregnancies; in four of these women, etiologies for the seizures were found on history or evaluation. Whether "gestational epilepsy" is a true entity or simply a statistical quirk cannot be answered at this time. For clinical purposes, a woman who has a noneclamptic seizure during pregnancy should be appropriately evaluated for an underlying cause. The effect of pregnancy on the seizure frequency of a known epileptic woman is variable. In a review of 27 studies from 1884 to 1980, Schmidt[11] found an increased incidence of seizures in 24% of 2,165 pregnant women, a decreased incidence in 23%, and no change in 53%. Knight and Rhind,[12] in an analysis of 60 patients, found that if the seizure frequency before pregnancy was >1/month, there was a 98% chance that the seizure frequency would increase during pregnancy; if the seizure frequency was <1/month before pregnancy, only 25% experienced an increased seizure frequency. Similarly, Remillard et al[13] found that 75% of women with a seizure frequency of >1/month before pregnancy had an increased seizure frequency during pregnancy. The prospective study by Schmidt et al[14] is worthy of attention. Of 136 pregnancies in 122 epileptic women, these investigators found no change in seizure frequency in 50%, and a decrease in 13%. In most women, increased seizure frequency could be attributed to medication noncompliance or sleep deprivation. These authors concluded that pregnancy itself had little effect on seizure frequency. Otani[15] found that in 80% of compliant pregnant epileptics there was no change in seizure frequency and only 16% had an increase.

In a recent prospective study of 140 pregnant epileptic women, Bardy[16] found that 31% remained seizure-free, 14% showed a decrease in frequency, 23% no change, and 32% had an increase in seizure frequency. The greatest number of convulsions occurred in the last trimester. Bardy[16] could not find a factor to explain these changes. It should be pointed out that although anticonvulsant levels were measured monthly, no changes in therapy were made (despite falling serum levels) unless the patient had seizures; i.e., there was no preventive intervention. In Robertson's[4] careful prospective study of 64 epileptic women on monotherapy followed with frequent anticonvulsant blood level determinations and adjustments of anticonvulsant dosages, only 5% had an increase in seizures during pregnancy; 26% had a decrease, and 69% had no change in seizure frequency. From these reports it would appear that the majority of women who have infrequent seizures will not experience an exacerbation of seizures if they are compliant with their medication program, if anticonvulsant levels are closely monitored, and if appropriate dosage changes are made before seizures occur. Although there are hormonal and metabolic alterations in antiepileptic drug dispositions in pregnancy, no single change appears to be responsible for differences in seizure frequency.[11] Fortunately status epilepticus occurs in less than 1% of pregnant epileptics.[1]

EPILEPSY AND PREGNANCY COMPLICATIONS

Andermann et al[17] studied the complications of pregnancy in epileptic women at the Montreal Neurologic Institute. They found no increase in bleeding, spontaneous abortion, prematurity, or toxemia, as well as no change in duration of labor or incidence of breech presentation. Overall they found no difference in birth weights of infants born to epileptic women compared to controls; they noted, however, that if weights were adjusted for time of gestation, there was evidence of intrauterine growth retardation. While perinatal mortality was increased threefold over the general population, there was no increase in infant mortality. In a review of outcome of pregnancy in epileptic Norwegian women, Egenaes[18] found a small but statistically significant increase in bleeding and ablatio placentae, but no increase in the incidence of hyperemesis gravidarum or toxemia. He attributed the increased incidence of bleeding to treatment with anticonvulsant drugs and not to epilepsy per se.

In a recent study, Yerby et al[19] matched pregnant epileptics and pregnant nonepileptic controls in Washington state for a variety of factors, including socioeconomic status, marital status, age and race. They found an increased frequency of preeclampsia, amniocentesis, induced labor/cesarean section, low birth weight, and low Apgar scores in the epileptic group. A significant number of infants with low Apgar scores developed asphyxia. There was also an increased risk of previous fetal loss after 20 weeks of gestation. Of interest was the finding of no increased rate of fetal malformation. Unfortunately in this study it was not known whether the women with epilepsy were treated or not, and no details of the quality of prenatal care were given.

Nelson and Ellenberg,[10] in their review of maternal seizure disorders and pregnancy outcome, found that stillbirth, microcephaly, mental retardation, and non-

febrile seizure disorders occurred with an increased frequency in epileptic mothers as compared to nonepileptic controls. In the same study, toxemia and first and third trimester bleeding were significantly higher in incidence in the epileptic group; there was no significant difference for placenta previa, abruptio placentae, hyperemesis gravidarum, polyhydramnios, or hemorrhagic shock. On a review of these studies, it would appear that there is no consistent increase in the complication rate of pregnancy in epileptic women although in selected studies, a statistical difference may be found for a given complication. Such exceptions may be ablatio placentae, perinatal mortality, and low birth weight relative to gestational age. All of these studies were retrospective except that of Andermann et al,[17] which contained a mixture of retrospective and prospective data.

A small prospective study of 59 pregnant patients with epilepsy was reported by Battino et al.[20] These women were followed closely before and during pregnancy. The only complication noted was a vaginal hemorrhage in one patient (1.7% incidence of complications). The incidence of spontaneous abortions was 6.6% and of prematurity 3.3%; both of these figures were lower than those for the Italian population at large.[20]

Because of relatively small differences in complication rates between epileptic and nonepileptic women, only a large study could detect significant differences. This would require a large prospective study from a single institution in which good neurologic and obstetric care is given. The logistics are difficult, and the "ideal study" may never be done.

ALTERATIONS IN METABOLISM OF ANTIEPILEPTIC DRUGS DURING PREGNANCY

During pregnancy, a change takes place in the pharmacokinetics of many, if not all, anticonvulsant medications. The precise reasons for these alterations are not clear, and a number of different factors are undoubtedly at work. In general terms, the changes may reflect differences in absorption, distribution, protein binding, and metabolism. Variations in compliance and significant weight gain are other important factors. Philbert and Dam[21] and Levy and Yerby[22] recently reviewed the effect of pregnancy on antiepileptic drug utilization. Phenytoin clearance increases in almost all patients during pregnancy. The alteration may begin early and progress throughout pregnancy before values return to normal 3 months after delivery.[23]

As noted by Levy and Yerby,[22] the effect of pregnancy on phenobarbital and primidone clearance is more variable, but most women demonstrate increased phenobarbital clearance and falling plasma levels on constant phenobarbital dosages. No consistent changes in primidone clearance occur during pregnancy, but the level of derived phenobarbital consistently falls.

While there is a tendency for increased carbamazepine clearance during pregnancy, this change is variable and usually not significant, at least in patients on monotherapy.[23–25]

Philbert et al[26] found a sudden drop in serum valproate levels just before term and a marked increase immediately after delivery in four women on valproate monotherapy. A gradual decline in serum valproic acid levels was found in 26 women as pregnancy progressed. During the first and second trimester, the free fraction was found to remain constant at approximately 10%; during the last trimester, it increased up to threefold at the time of parturition.[27] This change may have been responsible for a high incidence (50%) of fetal distress at birth.

In another study, no definite trend was seen in blood levels of ethosuximide in ten pregnant women followed during pregnancy.[28]

TERATOGENESIS AND ANTICONVULSANTS

In 1964 Janz and Fuchs[29] asked, "Are antiepileptic drugs harmful when given during pregnancy?" In their study, in which 246 epileptic mothers were mailed a questionnaire, there were no controls. The reported incidence of malformations was no greater in epileptic women taking anticonvulsants than in the population at large.[29] However, the discussion is not yet concluded. In his review of the problem, Janz[30] noted that in several prospective studies, malformations of children of mothers without epilepsy were seen in 5.7% of the cases but in 11.1% of the children of mothers with epilepsy; in retrospective studies, the respective figures were 2.7% and 5.1%. In other words, the incidence of malformations was approximately twice as high in epileptic mothers as in controls.

To further complicate the matter, Janz[30] noted that several studies had found the incidence of malformations in children of epileptic fathers to be increased, but not as much as in the children of epileptic mothers. In the same review, he also found that in a series of 15 retrospective studies the incidence of malformations was 3.4% in untreated epileptic mothers and rose to

7.8% in treated epileptic mothers.[30]

In a more recent review, Kelly[31] summarized the rate of malformation in 16 studies. He noted an incidence of 17.86% malformations in infants of treated epileptic mothers, 5.00% in infants of untreated mothers, and 2.14% in infants of control mothers. As he points out, most of the studies did not use actual controls, but only data from population studies. Dansky et al[32] have shown an increased risk of malformation to be associated with higher plasma levels of phenytoin or barbiturates. Whether or not the apparent increase of malformations in children of epileptic mothers is due to genetic factors associated with epilepsy, environmental agents (especially anticonvulsants), or an interplay between both cannot be stated with certainty. One might predict that polytherapy may be associated with a higher incidence of malformation than monotherapy, but this is not proven. Most probably a complex interaction between the genetics of epilepsy, the anticonvulsants, and the genetic determinants of anticonvulsant metabolism is responsible.[33]

Do anticonvulsants produce specific malformations? Cleft lip, with or without cleft palate, and congenital heart defects are the most common malformations; both have been found in children of mothers taking a variety of anticonvulsants.[30,31] Malformations which occur less frequently in infants of treated epileptic mothers include skeletal abnormalities such as club foot; gastrointestinal, such as anal atresia or diaphragmatic hernia; urogenital, including hypospadias; and central nervous system, with microcephaly, meningomyelocele, and anencephaly.[30]

Hanson and Smith[34] suggested that hydantoin medications could produce a characteristic syndrome in infants born of mothers taking these medications. In addition to the major malformations described above, they found a relatively high incidence of minor anomalies including hypertelorism, short nose, low set ears, ptosis, fingernail hypoplasia, and hypoplasia of the distal finger digits. Such anomalies may be found in up to 30% of infants exposed to hydantoins in utero.[31] Janz[30] points out, however, that these same anomalies may be seen in infants of mothers taking anticonvulsants other than hydantoins and even in infants of epileptic mothers taking no drugs.

Zackai et al[35] reported on the children of three mothers who took trimethadione during pregnancy. The pattern of malformations in these children and those of two women previously reported by German et al[36] formed the "fetal trimethadione syndrome." The common features of this syndrome included mild retardation, speech difficulty, V-shaped eyebrows, epicanthus, low set backward sloped ears, palatal anomalies, and dental irregularities. Whether or not these anomalies are specific for trimethadione is debatable.[30,31] What seems clear, however, is that the incidence of fetal malformations in mothers taking trimethadione is unacceptably high. In Kelly's review,[31] 65 reported instances of fetal exposure to trimethadione or paramethadione were noted; and a normal child was "the exception." Since more effective and less toxic medications for absence epilepsy are available, there is no reason to use trimethadione in women who may become pregnant.

Infants exposed to valproic acid during the first trimester of pregnancy have a 1% to 2% incidence of neural tube defects, especially spina bifida.[37,38] In addition, minor facial anomalies including brachycephaly, high forehead, shallow orbits, flat nose, hypertelorism, long upper lip, small mouth, and low set ears have been seen with valproic acid treatment. Other anomalies such as hypospadias and long, thin, overlapping fingers and toes have been called distinctive for this anticonvulsant.[27] If other choices of anticonvulsants are available, women who intend to become pregnant should probably not be treated with valproic acid. If the drug is used in pregnancy, screening for neural tube defects with serum alpha fetoprotein and uterine ultrasound are advised.

Not enough information about the teratogenicity of ethosuximide is available to enable one to draw any conclusions. In one small series, two of 13 infants were born with cleft lip to mothers taking ethosuximide.[28]

The mechanisms by which anticonvulsants may induce malformations are unknown. In a recent prospective study of 46 epileptic women, Dansky et al[39] found blood folate levels in pregnancies with abnormal outcomes to be significantly lower than those in pregnancies with normal outcomes. No such relationship was found in a study of 125 epileptic pregnant women by Hiilesmaa et al.[40] Robertson[4] states that folic acid supplementation greater than 5 mg is not required in the management of pregnant epileptics.

HEMORRHAGIC DISEASE OF THE NEWBORN AND ANTICONVULSANTS

Bleeding tendencies have been reported in newborns of women taking anticonvulsants. This effect is due to decreased levels of vitamin K-dependent clotting factors and can be prevented by administering phytona-

dione (vitamin K) before birth. In a retrospective study of 115 infants of epileptic mothers, Vert and Deblay[41] found that eight had hemorrhagic disorders (five liver hematomas, one cerebral hemorrhage, and two gastrointestinal bleeding). The prothrombin time was at or below 20% in 28% of the newborns of mothers taking phenytoin and/or phenobarbital. In this study, prothrombin time at birth was at a mean of 90.5% in 14 infants of epileptic mothers treated with 20 mg of vitamin K for 2 weeks before delivery. The neonate should be given 1 mg of parenteral vitamin K at birth.

ANTIEPILEPTIC DRUGS IN NEWBORN SERUM

Concentrations of phenobarbital, phenytoin, primidone, carbamazepine, and diazepam in newborn serum are similar to maternal serum concentrations.[42] The concentration of valproic acid in cord blood has been found to be increased from 145% to 219% when compared to the mother's serum level.[26] At birth, fetal and maternal concentrations of ethosuximide are similar.[28]

The biological half-life of anticonvulsants is frequently greater in neonates: phenobarbital, 40 to 500 hours; phenytoin, 15 to 105 hours; carbamazepine, eight to 28 hours; valproic acid, 14 to 88 hours; ethosuximide, 40 hours; and diazepam, 40 to 400 hours.[42]

Neonatal depression at birth has been associated with anticonvulsant use by the mother, especially with phenobarbital, phenytoin, and diazepam. The symptoms are present at birth and clear in a few days. Depression may be seen in 5% to 10% of such births.[42] Withdrawal symptoms consisting of crying, sleep disturbance, myoclonic jerks, tremors, hyperactivity, vomiting, sneezing, and yawning have been seen in up to 20% to 66% of infants of mothers taking phenobarbital, phenytoin, and benzodiazepines. The symptoms may be prolonged and last for weeks.[42] In a prospective study in Manchester, 18% of infants born to epileptic mothers experienced neonatal jitteriness; the percentages were the same whether or not the mother was receiving anticonvulsants.

BREAST FEEDING

The concentration of anticonvulsants in breast milk varies inversely with the degree of protein binding in blood. Anticonvulsants do not bind to breast milk protein[43]; it is only the free fraction, therefore, which appears in breast milk. The amount of anticonvulsant in breast milk in relationship to plasma concentration is 5% for valproic acid, 17% for phenytoin, 35% for phenobarbital, 40% for carbamazepine, 80% for primidone, and 97% for ethosuximide.[43] If one assumes a 1 liter intake by the infant, the baby would ingest 5 mg of valproic acid, 22.8 mg of phenytoin, 14 mg of phenobarbital, 4 mg of carbamazepine, 9.6 mg of primidone, and 97 mg of ethosuximide.[43] With the possible exception of ethosuximide, these amounts are almost negligible and can be ignored unless the infant develops symptoms.

TREATMENT OF MATERNAL STATUS EPILEPTICUS

Status epilepticus in the pregnant woman should be treated as aggressively as it is in other patients. The approach should include establishing a clear airway and securing an intravenous (IV) line. Blood for routine chemical and anticonvulsant levels should be obtained. An infusion of phenytoin 18 mg/kg should be started and infused at a rate no greater than 50 mg/minute. High-dose phenytoin infusions were given to 24 women with moderate to severe preeclampsia without significant side effects either to the mother or to the fetus.[44] During a continuous generalized tonic-clonic seizure, there should be no hesitation in administering IV diazepam 10 to 20 mg to abort the seizure even though there may be some fetal depression because of the rapid placental transfer of diazepam.

PREVENTION OF PREGNANCY

It may be appropriate to end with a brief discussion of prevention of pregnancy in women taking anticonvulsants. Mattson et al[45] recently reviewed the subject. There is no evidence that oral contraceptives exacerbate seizures, but there *is* evidence of a higher incidence of oral contraceptive failure. The mechanism for the increased failure rate is enhanced metabolism of the oral contraceptive agent because of anticonvulsant-enhanced enzymatic induction. This effect is more critical for the "mini pill." If a higher degree of protection is required, a medium-dose oral contraceptive should be prescribed initially although there are more side effects and more risk with the higher-dose preparations. Breakthrough bleeding may be a warning of decreased contraceptive efficiency. Alternate meth-

ods of contraception may be suggested in these instances.[45]

SUMMARY

Given the advantages of modern medical management, most pregnant epileptic women should experience no significant increase in seizure frequency. With good prenatal medical and obstetric care, complications of pregnancy and delivery in epileptic women differ little from those in the general population. In any case, monotherapy should be employed if possible, and anticonvulsant levels should be monitored closely during pregnancy and immediately after delivery. Dosage adjustments should be made appropriately. Since such an adjustment will usually be made in the second or third trimester, one would not expect it to produce an increased number of malformations. Trimethadione should be absolutely avoided and valproic acid used only with caution and with monitoring of alpha fetoprotein and uterine ultrasound. Although it is true that there is an increased incidence of malformations in children of epileptic women (with or without anticonvulsants), the great majority of these babies are normal.

Vitamin K should be given to the mother before delivery, and the newborn should receive 1 mg vitamin K at birth. Unless the infant becomes symptomatic, breast feeding should be allowed.

If seizures occur for the first time during pregnancy, the patient should be appropriately evaluated. Status epilepticus in pregnant women calls for aggressive and careful treatment. Finally, it should be remembered that oral contraceptives, especially the "mini pill," have a higher failure rate in women taking anticonvulsants. Discussing this problem with the patient is helpful.

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