

Epilepsy and Pregnancy

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SUMMARY: *The management of the pregnant epileptic requires close cooperation between the neurologist and obstetrician. To prevent complications, knowledge is required about the natural history of epilepsy during pregnancy, the possible teratogenic effects of antiepileptic drugs, and changes in their absorption, biotransformation, and excretion. Close plasma antiepileptic drug monitoring is required because of the change in the handling of antiepileptic drugs during pregnancy. The treatment of status epilepticus with intra-*

venous phenytoin is effective. Drug interactions which may lead to toxic plasma levels of some drugs and subtherapeutic plasma levels of others should be anticipated. The risk of problems resulting from antiepileptic drug therapy during pregnancy appears to be minor, provided that proper medical supervision is available. Newer antiepileptic drugs should not be administered to the pregnant epileptic until their safety in pregnancy is fully established.

RÉSUMÉ: *Le traitement de l'épileptique enceinte requière une collaboration étroite entre le neurologue et l'obstétricien. Afin d'empêcher les complications, il faut connaître l'histoire naturelle de l'épilepsie pendant la grossesse, les effets tératogènes possibles des médicaments antiépileptiques, et les modifications dans l'absorption, la biotransformation et l'excrétion de ces drogues. Il est extrêmement important de suivre le niveau plasmatique des drogues à cause des changements qui se produisent dans leur maniement pendant la grossesse. Le traitement du status*

épileptique avec phénytoïn intraveineux est très efficace. Il faut s'attendre à des interactions médicamenteuses qui peuvent produire des niveaux plasmatiques toxiques de certains médicaments ou des niveaux sous-thérapeutiques pour d'autres. Il semble bien qu'il y a un risque mineur de problèmes avec les antiépileptiques pendant une grossesse, à condition que la patiente soit bien suivie médicalement. On ne devrait pas administrer de nouveaux anticonvulsivants aux épileptiques enceintes avant d'en connaître à fond leur sécurité.

INTRODUCTION

Pregnancy in the epileptic patient poses special problems that require close cooperation between the neurologist and obstetrician. This will generally result in a successful and an uncomplicated course for the developing fetus. Over the last ten years, advances in the treatment of epilepsy with newer anticonvulsants and new knowledge acquired about older antiepileptic drugs have added greatly to the physician's ability to treat epilepsy. The development of analytical techniques for the monitoring of antiepileptic drug levels has contributed considerably to the prevention of dose-related toxic side-effects and has given new information about potentially serious drug interactions which cause toxic plasma levels of some drugs and subtherapeutic levels of others.

The effect of pregnancy on epilepsy has been studied in the past with conflicting results. (Baptisti, 1938; Burnet, 1946; Sabin and Oxorn, 1956; Dimsdale, 1959; Suter and Klingman, 1957; Knight and Rhind, 1975). Various factors have been proposed to explain a change in seizure frequency during pregnancy, however, these do not predict the course of epilepsy during gestation. The effect of seizures on the developing fetus has also been considered, and controversy still exists as to whether antiepileptic drugs are teratogenic.

In the first encounter with the pregnant epileptic, genetic counseling is appropriate to alleviate the parents' anxiety as to the risk of their child having epilepsy. The risk varies depending on whether the mother has idiopathic or symptomatic epilepsy. Hill (1963) stated that if the marital partner's EEG was normal and the family histories negative, the chances that a child of the marriage will be

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epileptic were not more than 1 in 40, if the patient's epilepsy was acquired. The risk of epileptic offspring increases, depending on the presence of genetic factors in the idiopathic seizure disorders (positive family history, 3 per second spike and wave discharges characteristic of idiopathic epilepsy). The role of heredity in epilepsy has not been clarified because of inherent problems in investigation. Metrakos and Metrakos (1961) have studied the genetic factors extensively and concluded that eleven percent of the offspring have the epileptic trait. The electroencephalographic 3 per second spike and wave characteristic is inherited as an irregular autosomal dominant trait. The overall risk to a child of developing clinical epilepsy when one parent is epileptic is between 2 and 3 percent. Taking these factors into consideration, pregnancy should not be discouraged and support should be given. If the father also has idiopathic epilepsy, the risk for the offspring may be as high as 20 to 25 percent.

NATURAL HISTORY OF EPILEPSY DURING PREGNANCY

Seizure frequency during pregnancy will either increase or remain unchanged. (Baptisti, 1938; Burnet, 1946; Suter and Klingman, 1957; Knight and Rhind, 1975). Few patients have a decreased seizure frequency. In any individual patient the course, however, is unpredictable and no reliable factors allow an accurate prediction of the natural course of seizure control during gestation and the puerperium (Dimsdale, 1959).

The pregnant patient may have a previous history of recurrent seizures and anticonvulsant therapy or may present with seizures for the first time during gestation. Knight and Rhind (1975) reported three groups of patients with seizures related to pregnancy: true gestational epilepsy with seizures occurring only in relation to pregnancy, idiopathic epilepsy with the diagnosis established in the majority of patients prior to their first pregnancy, and symptomatic epilepsy with seizures complicating structural brain disease. The majority of their patients had idiopathic epilepsy.

Knight and Rhind observed that 45.2% of patients with idiopathic epilepsy had an increased seizure frequency, 50% experienced no change, and only 4.8% had a decreased incidence. No correlation was made between the degree of seizure control and antiepileptic drug levels and no statement can be made regarding improved seizure control with antiepileptic drug monitoring.

In patients with gestational epilepsy, the occurrence of seizures in one pregnancy was no guide to the course of seizure control in subsequent pregnancies. Thirty-one percent of this group of patients experienced recurrent seizures during the same pregnancy, while 69% had a single grand mal seizure.

In 29% of symptomatic patients an identifiable cause for the seizures was found. In the patients with idiopathic and symptomatic epilepsy, the increased frequency of seizures occurred most commonly during the first trimester. The only prognostic factor which affected epilepsy during pregnancy was the frequency of seizures before pregnancy. A likelihood of increased seizures during pregnancy with a male fetus was also observed. Some reports claim an exacerbation of seizures during pregnancy in patients with a history of menstrual exacerbation (Dimsdale, 1959). No correlation exists with the age of onset of seizures, maternal age, type of seizure disorder, and course during a previous pregnancy (Dimsdale, 1959; Knight and Rhind, 1975).

The electroencephalographic changes that occur during pregnancy have not been well studied and the causes of the observed changes are even less clear. However, Gibbs and Reid (1942) reported a higher incidence of abnormal electroencephalograms in normal pregnant patients than in normal nonpregnant controls. Logothetis et al. (1959) observed activation of electroencephalographic abnormalities in 11 of 16 patients injected with conjugated estrogens.

Hormonal changes that occur during pregnancy have received attention as important parameters in the change in frequency of seizures. (Wolley and Timiras, 1962a & b; Marcus et al., 1966; Timiras, 1969;

Backstrom, 1976). Estrogens rise gradually throughout the course of pregnancy while progesterone has a biphasic pattern of secretion with an initial phase at approximately four weeks of gestation. Estrogens are epileptogenic in experimental animals and progesterone has both antiepileptic and convulsant properties. The high output of steroid and protein hormones from the placenta (mainly estrogen) stimulates the synthesis of certain hormone-transport proteins which may also influence antiepileptic drug binding. The effects of sex hormones are given as explanations for the exacerbation of seizures in relation to the phases of the menstrual cycle. Increased estrogenic activity during the immediate premenstrual phase is thought to be the most significant factor. It is important to note, however, that no relationship exists between changes in seizure frequency during pregnancy and the menstrual cycle (Knight and Rhind, 1975). The role of increased aldosterone secretion and water retention is uncertain.

DRUG TREATMENT

The factors which cause a change in seizure frequency are not clearly understood, but these must be multifactorial since the natural history of seizures during pregnancy is variable. The most important consideration is the change in the handling of antiepileptic drugs during pregnancy. Important changes in absorption, biotransformation, distribution, and excretion of antiepileptic drugs may have marked influence on seizure control during pregnancy (Mygind et al., 1974; Lander et al., 1977; Ramsay et al., 1978).

Plasma phenytoin levels decrease during pregnancy despite constant oral phenytoin dosage. Phenytoin is absorbed in the duodenum, metabolized primarily to p-HPPH in the liver, and conjugated with glucuronide (Glazko, 1973; Gabler and Hubbard, 1973; Peterson and Zweig, 1974). This conjugated form is actively secreted into the renal tubules and eliminated in the urine. Non-bound phenytoin is filtered in the renal glomerulus and partially reabsorbed. In normal

subjects taking phenytoin, 68 to 93 percent of a daily oral dose is found in urine as p-HPPH and 1.0 to 1.6 percent as unmetabolized phenytoin (Glazko et al., 1969; Dilantin Monograph, 1973). Essentially no p-HPPH is found in feces.

Pregnancy causes a significant decrease in the hepatic enzymatic activity of aniline hydroxylase and ethylmorphine N-demethylase (Guarino et al., 1969). Gabler and Hubbard (1973b), using pregnant rhesus monkeys, found 67 percent increase in the half-life of phenytoin administered intravenously. However, Devi et al. (1973) found intestinal malabsorption as assessed by d-xylose absorption, Schilling test, and 72-hour stool fat content in 50 percent of normal and all anemic women tested between 2 and 6 days postpartum. Ramsay et al. (1979) studied 15 pregnant epileptics. They found seizure exacerbation in 14, with constant IV phenytoin half-life, constant urinary p-HPPH, and increased quantity of stool phenytoin accompanied with biochemical signs of intestinal malabsorption. The authors concluded that intestinal malabsorption played a major role in the observed decrease in serum phenytoin associated with pregnancy.

We recommend that the close supervision of the pregnant epileptic include frequent assessment of serum levels of antiepileptic medications. The documented decrease in plasma phenytoin levels during pregnancy may cause seizure exacerbations along with fluid retention and hormonal changes. Counteraction of intestinal malabsorption of phenytoin should be anticipated by assessment of serum levels and administration of additional oral medication.

Decreased compliance due to nausea, delayed or decreased absorption due to intestinal stasis and vomiting, increase in volume of distribution of antiepileptic drugs during pregnancy, electrolyte changes, mild alkalosis that occurs during the latter course of pregnancy, emotional stress, and hormonal changes may be contributing factors. The role of folic acid supplementation during pregnancy is unclear. Experimentally, folic acid has convulsant properties when applied to the cerebral cortex

(Mauguiere et al., 1975) and some workers believe that antiepileptic drugs have an anti-folate effect (Woodbury and Kemp, 1971; Reynolds, 1973; Smith and Racusen, 1973).

TREATMENT OF STATUS EPILEPTICUS

Gestationally-related status epilepticus is rare, however, it carries a high risk (Goodwin and Lawson, 1947; Klein et al., 1956). Knight and Rhind (1975) reported two cases in 53,000 deliveries; Klein et al. (1956) observed two cases in 52,000 deliveries at the Morrisania Hospital. Ramsay et al. (1978) reported the successful management of one such patient with intravenous phenobarbital, phenytoin, and paraldehyde. Many reports have advocated the use of benzodiazepines for the treatment of status epilepticus. Although a single IV dose of diazepam will control seizures in 60 to 80% of patients, approximately 50% of these patients will require additional IV doses of diazepam to control breakthrough seizures. Wallis et al. (1968) McWilliam and Leads (1958) and Wilder et al. (1977) have reported effective control of status epilepticus with IV phenytoin. We recommend obtaining control of airway and oxygenation, establishment of a reliable intravenous line, and use of IV anticonvulsants, particularly phenytoin, to control status epilepticus in the pregnant patient.

DRUG INTERACTIONS

Drug interactions between antiepileptic drugs and other concurrently administered drugs during pregnancy may have important implications in seizure exacerbation. Antiepileptic drug levels may be decreased by antacids (interfering with absorption), antihistamines, diazepam, ethanol, and chlordiazepoxide. Interaction between individual anticonvulsants may lead to toxic or subtherapeutic effects. Carbamazepine may lower phenytoin levels. Drugs which may at times be indicated during pregnancy and which cause an elevation of

phenytoin levels include dicoumarol, INH, and chloramphenicol.

ANTIEPILEPTIC DRUGS AND TERATOGENESIS

Three types of disorders have been described in infants born to mothers who receive antiepileptic drug therapy during pregnancy: congenital malformations, chromosomal aberrations, and coagulation defects. There is an increased incidence of congenital malformations in the children of epileptic mothers (Spiedel and Meadow, 1972; Fedrick, 1973; Lowe, 1973; Bjerkedal and Bahna, 1973; Higgins and Comerford, 1974; Janz, 1975). Many of the commonly used anticonvulsants cross the placenta (Perlman, 1967; Mirkin, 1971; Waddell and Mirkin, 1974; Rane et al., 1974) and it is possible that they have a teratogenic effect. The increased incidence of malformations could be the result of either a direct or genetic effect of the maternal epilepsy on the fetus and/or the effects of antiepileptic drugs.

Congenital malformations occur with a higher frequency in the offspring of epileptic mothers treated with antiepileptic drugs during pregnancy than in offspring of epileptic mothers not receiving antiepileptic drugs during pregnancy. Published studies on congenital anomalies reveal an incidence of 2.5% in offspring of non-epileptic mothers, a 4.2% incidence in untreated epileptic mothers and a 6% incidence in drug-treated epileptic mothers (Spiedel and Meadow, 1972; Janz, 1975). In addition to having an increased risk of congenital malformations, epileptic mothers have an excess of complications during pregnancy and labor (Bjerkedal and Bahna, 1973).

The increased risk of congenital malformations is manifested as an increase in orofacial cleft defects and a less significant increase in heart lesions. Other reported malformations include skeletal abnormalities, central nervous system anomalies, hypospadias, and intestinal atresia.

One of the difficulties in the interpretation of data on antiepileptic drug teratogenesis is that group differences may be partially responsible for some of the observed defects.

Socioeconomic backgrounds of nonepileptic mothers are difficult to match with those of epileptic mothers. Age and complications during pregnancy may also differ. Thus, concurrently available data do not permit the unequivocal assumption that antiepileptic drugs are to be wholly implicated in teratogenicity. In the clinical situation, all the major antiepileptic drugs have been implicated. The mechanism of malformation is unknown but may be related to induced chromosomal anomalies and/or folate deficiency. Grosse et al. (1972) showed that the rate of structural chromosomal abnormalities in mothers and their children who were exposed to antiepileptic drugs in utero was significantly higher than in paired controls. DeVore and Woodbury (1977) proposed that the teratogenic effects of phenytoin could be related to increased serum and tissue concentrations of the drug which may be observed during pregnancy in addition to its effect of decreasing maternal serum folate.

Many questions remain unanswered but the risk of problems resulting from anticonvulsant drug therapy during pregnancy would appear to be minor provided that proper medical supervision is available. Newer antiepileptic drugs like valproic acid should not be administered during pregnancy.

Maternal treatment with antiepileptic drugs may cause neonatal hematological effects which are not teratogenic in nature, but warrant consideration since fatal hemorrhage may result. (Van Crevald, 1958; Douglas, 1966; Alagille et al., 1968; Mountain et al., 1970; Solomon et al., 1972; Solomon et al., 1974; Bruni, et al., 1979). The infants may show clinical signs of bleeding secondary to a deficiency in vitamin K dependent clotting factor (II, VII, IX, X). The coagulation defects usually become apparent in the first 24 hours and the clotting parameters are similar to those observed in hemorrhagic disease of the newborn in which bleeding generally occurs later during the second to fifth day of life. Clinically, hemorrhage may be intraperitoneal, intrathoracic, or intracranial. Phenytoin, phenobarbital, and primidone, alone or in combination, may be

responsible. The coagulopathy can be reproduced in experimental animals (Van Crevald, 1958; Solomon et al., 1972; Solomon et al., 1974) and it is possible that the mechanism is due to hepatic microsomal enzyme induction by antiepileptic drugs.

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