

## AMERICAN ACADEMY OF PEDIATRICS

Committee on Drugs

### Anticonvulsants and Pregnancy\*

The Committee on Drugs of the American Academy of Pediatrics clearly supports the accepted principle that *no* drug should be given to the pregnant woman unless it is necessary for her health or for the well-being of the fetus. If medication must be given during pregnancy, physicians should use the most efficacious drug that is known to have the least risk to the fetus; and this drug should be used in the lowest, effective dose. Some drugs (such as anticonvulsants), even when they are used with care, may result in an increased risk to the fetus; but they are necessary for the mother's health.

#### TERATOGENIC POTENTIAL

Many drugs have teratogenic potential when given to the appropriate animal in sufficient dosage and at a critical period in pregnancy. It is difficult to make definite predictions of the effects of a given drug on the human fetus based on experimental animal data because of the marked species variability. Detection of the human teratogenic potential of a drug depends on the frequency with which the drug is used during pregnancy, the severity of the malformations produced, and the rate of spontaneous occurrence of similar malformations.

The potential teratogenicity of anticonvulsants, such as phenobarbital and phenytoin sodium (diphenylhydantoin), for humans has only recently been recognized, despite the widespread and long-term use of these drugs.<sup>1</sup> This long delay in recognition may be partly because of the small number of pregnant women with epilepsy (3 per 1,000) and the subtle nature of many of the "malformations" produced. However, recent articles have suggested a "fetal hydantoin syn-

drome"<sup>2,3</sup> and a similar "syndrome" after barbiturates,<sup>4,5</sup> alcohol,<sup>4,6</sup> and trimethadione.<sup>7</sup>

#### Hydantoins

What are the risks of hydantoins to the fetus? Major malformations, such as cleft lip and palate and congenital heart disease, have been documented in animal studies<sup>8</sup> and in humans.<sup>9</sup> The incidence of congenital heart disease in the general population is approximately 5 per 1,000 births, and the incidence of cleft lip/palate is approximately 2 per 1,000 births. In the children of women with epilepsy (who are usually on anticonvulsants), the incidence of congenital heart disease and of cleft palate are both approximately 18 per 1,000 births (Table). Thus, the infant of a woman with epilepsy on anticonvulsants apparently has a two to three times greater risk of congenital heart disease and a five to ten times greater risk of cleft palate than the general population.

From the currently available data it is not clear whether the increased risk of malformation is caused by (1) epilepsy in general or by particular types of epilepsy, (2) a common, genetic predisposition to epilepsy and the malformation, (3) a genetic difference in pharmacokinetics and drug disposition, (4) specific drugs, or (5) deficiency states in the mother or fetus induced by specific drugs.

However, there may be multifactorial genetic interrelationships between cleft lip/palate and congenital heart disease. A genetic association of cleft lip/palate with epilepsy may be unrelated to anticonvulsants.<sup>9</sup>

A further constellation of "malformations" that occurs in 11% of infants exposed to phenytoin in utero has been termed the *fetal hydantoin syndrome*.<sup>2,10</sup> The most consistent findings in this syndrome have been prenatal growth deficiency, postnatal growth deficiency, microcephaly, and mental deficiency. Growth deficiency included microcephaly, small size at birth, and hypoplastic

\*The Committee on Obstetrics: Maternal and Fetal Medicine, American College of Obstetricians and Gynecologists, concur in these recommendations.

TABLE  
MALFORMATIONS PER 1000 BIRTHS BORN TO MOTHERS WITH AND WITHOUT EPILEPSY\*†

Population Studied	Total Number	All Malformations			Congenital Heart Disease			Cleft Lip/Palate		
		Number	Rate	Range	Number	Rate	Range	Number	Rate	Range
General population	606,673		27.5	19-35		...	4.1-5.7		1.6	1.5-2.7
Mothers with epilepsy on anticonvulsants	1,626	103	63	22-154	29	18	4-43	30	18.5	13-90
Mothers with epilepsy not on anticonvulsants	614	13	31	0-39	3	4-9	9-11	0	...	...

\*From Annegers et al.<sup>9</sup>

†This is a summary of data from multiple studies whose populations were collected in varying ways; therefore, the mean rates are meant only to give rough indications of incidence rather than firm numbers.

nails with abnormal dermal ridge patterns. Data were recorded on 104 children participating in the Collaborative Perinatal Project; the mothers of these children had been treated with hydantoins throughout pregnancy. Eleven of the children had a pattern consisting of at least three of the four major features.<sup>3</sup> Six of these 11 children had "mental deficiency" (IQ 31 to 84). Most of the children had one or more "dysmorphic features," which included such things as cafe au lait spots, hypopigmented nevi, inguinal hernia, and metatarsus varus. In a further review of 35 children born to 25 women treated with hydantoin during pregnancy, a broad or depressed nasal bridge was the only congenital abnormality that occurred in more than 50% of the children.<sup>3</sup> Despite this, the researchers felt that 11% of the infants exposed to hydantoin in utero will have a pattern of abnormalities with serious clinical consequences. It was unclear how many of these "minor" abnormalities were required to make a syndrome. Furthermore, it is not clear at what point the abnormalities are severe enough to be of "serious, clinical consequences."

The four major features—pre- and postnatal growth deficiency, microcephaly, and mental deficiency—are all interrelated, and they frequently are associated with intrauterine growth retardation even if hydantoins have not been used. Furthermore, it is difficult causally to relate hypopigmented nevi (which could be associated with tuberous sclerosis) or cafe au lait spots (which are associated with von Recklinghausen's disease) to fetal hydantoin exposure. Both tuberous sclerosis and von Recklinghausen's disease are genetic and are associated with seizures and mental retardation; however they are not related

to hydantoin exposure. Shapiro et al,<sup>11,12</sup> analyzing the same population from the Collaborative Perinatal Project, found that women with epilepsy had only a slight increase in major abnormalities, an increase that was unrelated to specific anticonvulsants. They ascribed the increased risk to epilepsy per se.

#### Other Anticonvulsants

Data on malformations caused by phenobarbital taken during pregnancy are even less conclusive than those on phenytoin. The incidence of major malformations, such as cleft lip/palate and heart disease associated with phenobarbital, would appear to be far less than that associated with hydantoins; but the incidence of all other abnormalities may be similar to that seen after the use of hydantoins.

There is scant information about the effects of other anticonvulsants on the fetus. Trimethadione has been reported to cause fetal malformations and mental retardation in a high proportion of those exposed,<sup>7</sup> and it should be avoided in pregnant women wherever possible. Carbamazepine has not been found to cause an increase in fetal malformations, but since the outcome of only 94 pregnancies has been reported,<sup>13</sup> more information is needed.

There are no data on the effects of valproic acid on the human fetus.

Some effects of anticonvulsants on newborn infants should be brought to the notice of physicians. Poorly substantiated reports suggest that infants born to mothers taking phenobarbital may become "jittery" because of barbiturate withdrawal. Further reports<sup>14</sup> indicate that infants exposed to phenytoin or barbiturates may have

depressed clotting factors and even neonatal hemorrhages, which are responsive to vitamin K.

### SUMMARY

There is an increased risk of congenital heart disease and cleft palate among the offspring of women with epilepsy, most of whom are on anticonvulsants. Part of this increase may be caused by phenytoin. The risk of all abnormalities in these infants appears to be about 4% to 5%, which is approximately double the rate of malformations in the general population. There appears to be an ill-defined "syndrome" associated with fetal exposure to hydantoin, although it has not been proven to be caused by the drug. The risk of this "syndrome" is of unknown magnitude, but it is probably less than 10%. The significance to a given child of the abnormalities in this "syndrome" is not predictable at this time.

### RECOMMENDATIONS

No woman should receive anticonvulsant medication unnecessarily. When possible, a woman who has been seizure free for many years should be withdrawn from her medication prior to pregnancy. When a woman who has epilepsy and requires medication asks about pregnancy, she should be advised that she has a 90% chance<sup>15</sup> of having a normal child, but that the risk of congenital malformations and mental retardation is two to three times greater than average because of her disease or its treatment. Women who seek advice later than the first trimester of pregnancy should be reassured with the foregoing figures rather than routinely urged to consider abortion. For these women, drug therapy should be continued throughout pregnancy because major anatomical malformations most likely would have taken place already, and the malformations associated with the hydantoin syndrome rarely have significant effect on the well-being of the child.

There is no reason at present to advise a woman to switch from phenytoin or phenobarbital to other anticonvulsants about which even less is known. Discontinuation of medication in a woman whose epilepsy is controlled by medicine may cause seizures, and prolonged seizures could cause serious sequelae to her and the fetus.

Physicians are often asked for recommendations about breast-feeding for mothers on anticonvulsant medications. A review of the published

literature shows that most anticonvulsants present in therapeutic levels in the mother also are present in breast milk. However, their concentration is low enough that there is little likelihood of any demonstrable effects on the infant. Thus, there is no evidence at the present time to suggest that a woman requiring anticonvulsants should either stop taking medication or avoid nursing.

COMMITTEE ON DRUGS

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### REFERENCES

1. Monson RR, Rosenberg L, Hartz SC, et al: Diphenylhydantoin and selected congenital malformations. *N Engl J Med* 289:1049, 1973.
2. Hanson JW, Smith DW: The fetal hydantoin syndrome. *J Pediatr* 87:285, 1975.
3. Hanson JW, Myrianthopoulos NC, Harvey MAS, et al: Risks to the offspring of women treated with hydantoin anticonvulsants, with emphasis on the fetal hydantoin syndrome. *J Pediatr* 89:662, 1976.
4. Hill RM: Fetal malformations and antiepileptic drugs. *Am J Dis Child* 130:923, 1976.
5. Bethenod MFA: Les enfants des antiépileptiques. *Pédiatrie* 30:227, April-May 1975.
6. Jones KL, Smith DW: Recognition of the fetal alcohol syndrome in early infancy. *Lancet* 2:999, 1973.
7. Feldman GL, Weaver DD, Lovrien EW: The fetal trimethadione syndrome: Report of an additional family and further delineation of this syndrome. *Am J Dis Child* 131:1389, 1977.
8. Martz F, Failing C III, Blake DA: Phenytoin teratogenesis: Correlation between embryopathic effect and covalent binding of putative arene oxide metabolite in gestational tissue. *J Pharmacol Exp Ther* 203:231, 1977.
9. Annegers JF, Elveback LR, Hauser WA, et al: Do anticonvulsants have a teratogenic effect? *Arch Neurol* 31:364, 1974.
10. Smith DW: Teratogenicity of anticonvulsive medications. *Am J Dis Child* 131:1337, 1977.
11. Shapiro S, Slone D, Hartz SC, et al: Anticonvulsants and parental epilepsy in the development of birth defects. *Lancet* 1:272, 1976.
12. Shapiro S, Slone D, Hartz SC, et al: Are hydantoins (phenytoins) human teratogens? *J Pediatr* 90:673, 1977.
13. Niebyl JR, Blake DA, Freeman JM, et al: Carbamazepine levels in pregnancy and lactation. *Obstet Gynecol*, to be published.
14. Bleyer WA, Skinner AL: Fatal neonatal hemorrhage after maternal anticonvulsant therapy. *JAMA* 235:626, 1976.
15. Hill RM: Letter to editor. *Am J Dis Child*, to be published.

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