Original Article

Wien Klin Wochenschr (2006) 118 [Suppl 2]: 12–16
DOI 10.1007/s00508-006-0539-8

WIENER KLINISCHE WOCHENSCHRIFT
The Middle European Journal of Medicine
Printed in Austria

The frequency of neonatal morbidity after exposure to antiepileptic drugs in utero

A retrospective population-based study

Silva Burja[1], **Zlatka Rakovec-Felser**[1], **Milena Treiber**[1], **Dušanka Hajdinjak**[2], and **Marijana Gajšek-Marchetti**[3]

[1] Department of Perinatology, Neonatology, Maribor Teaching Hospital, Maribor, Slovenia
[2] Department of Medical Statistics, Maribor Teaching Hospital, Maribor, Slovenia
[3] Medical Research Department, Maribor Teaching Hospital, Maribor, Slovenia

Summary. *Objectives:* To investigate the frequency of malformations, fetal growth retardation, cerebral hemorrhage and neonatal withdrawal symptoms in newborns exposed to antiepileptic drugs (AEDs) in utero.

Design: Population of the northeastern part of Slovenia (pregnant women and newborns between 1998 and 2002).

Methods: Data on newborns born between 1998 and 2002 of 37 epileptic mothers taking AEDs in pregnancy, of 32 epileptic mothers not taking AEDs in pregnancy and of 211 mothers healthy in pregnancy were ascertained from hospital obstetric and neonatal records and included in the study. The health status of 270 newborns was assessed. Main outcome measures: frequency of congenital malformations, growth retardation (SFD), intracranial hemorrhage, feeding problems and withdrawal symptoms.

Results: In the group not exposed to antiepileptic drugs (32 neonates), two (2.9%) had germinal matrix hemorrhage grade I, one (1.4%) was small for date (SFD) and one (1.4%) had feeding problems. In the group exposed to antiepileptic drugs (37 neonates), nine (13%) had germinal matrix hemorrhage grade I, six (8.6%) were SFD, five (7.24%) had feeding problems, four (5.8%) had withdrawal symptoms and three (4.3%) "macro" congenital anomalies. Among neonatal problems in the control non-exposed group of newborns of 211 healthy women we identified 23 (10.9%) newborns who were SFD, 5 (2.4%) cases with germinal matrix hemorrhage grade I, 5 (2.4%) cases with major congenital malformations and 7 (3.3%) cases with feeding problems.

Conclusions: Prenatal antiepileptic drug exposure in the setting of maternal epilepsy is associated with increased risk of neonatal morbidity. In our study a particularly significant connection was established between carbamazepine therapy during pregnancy and cerebral hemorrhage in the neonates.

Key words: Pregnant woman, epilepsy, antiepileptic drugs, high-risk neonate.

Introduction

Epilepsy is the most frequent neurologic disease in women during their fertile years, with a reported prevalence of 0.3–1% in pregnancy [1–4]. About 80% of pregnant epileptic women take antiepileptic drugs (AEDs) throughout their pregnancy despite teratogenic and other side effects on fetal development [5, 6]. The pregnancy itself rarely causes a deterioration of the disease: studies show that in 50% of cases the number of epileptic seizures remains unchanged, in 25% their number increases and in 25% it decreases [7]. Various metabolic changes may lead to a drop in AED concentration in the plasma of pregnant women, so adequate dosage of anticonvulsants is quite problematic, particularly as we must also keep in mind possible deleterious effects of the drug on fetal development. Several studies of birth outcomes in epileptic women show a two-to-three-fold increased risk of congenital malformations [8–10], but many of these studies did not include control groups [11]. Carbamazepine and valproate have been linked to neural-tube defects, whereas phenobarbital, phenytoin and primidone have been linked to congenital heart defects, cleft lip, and cleft palate [12]. Some studies found a tendency to growth retardation [13] and some found no sign of retarded growth [14–16]. Microcephaly has been reported in neonates with intrauterine exposure to AEDs. This is to be particularly expected in cases when the child's mother had taken phenobarbitone. The same study confirmed the association of the deleterious effect of phenobarbitone and phenytoin with a decrease in the child's learning abilities [17]. AEDs may also have other deleterious effects on the central nervous system of the fetus and newborn, such as passive addiction with neonatal withdrawal symptoms and intracranial hemorrhage [18]. On this background we examined the risk of malformations, fetal growth retardation, intracranial hemorrhage and passive addiction and feeding problems in the early neonatal period in a retrospective population-based study.

Material and methods

Data sources

All data on the newborns and their mothers were obtained from hospital neonatal and obstetric records at the Maribor Teaching Hospital Department of Perinatology. The northeastern part of the Perinatal Statistical Database of Slovenia (PERIS) was used to identify all epileptic women who gave birth at the Maribor Department of Obstetrics and their newborns in the 5-year period between January 1st, 1998 and December 31st, 2002. Maribor Teaching Hospital serves the total population of northeastern Slovenia, with approximately 2000 births per year. The midwives, neonatal nurses, doctors responsible for the deliveries and the neonatologists record the data on all births in PERIS. For our study of the stated 5-year period, we identified 69 pregnant women diagnosed as having "epilepsy" (37 had taken AEDs during pregnancy and 32 had not) and a randomized sample of 211 pregnant women who had received no prescription at all (with the only diagnosis "vaginal delivery") in the same period. Data on the main outcome measures of frequency of congenital malformations, growth retardation (small for date; SFD), intracranial hemorrhage, feeding problems and withdrawal symptoms were extracted from the Regional Hospital Discharge Registry. The data are transferred from the registry to PERIS, which records all discharges from all 14 Slovene perinatology departments. Discharge diagnoses were classified according to the International Classification of Diseases (ICD10).

Statistical analysis

We determined the incidence of neonatal problems in four groups of examined mother-newborn couples according to their exposure to the risk of AED side effects or the undesired effects of epilepsy itself. Group 1 comprised neonates of epileptic mothers exposed to one AED *in utero* (monotherapy), group 2 comprised neonates of epileptic mothers exposed to two or more AEDs *in utero* (polytherapy), group 3 comprised neonates of epileptic mothers not exposed to AEDs *in utero*, and group 4 comprised neonates of healthy mothers with the diagnosis "vaginal delivery". Because of the small number of subjects, we calculated the odds ratios with Fisher's test and the chi-squared test.

Results

Among the women giving birth in the 5-year period, 69 (0.7%) had epilepsy. From among these women 37 (53.6%) had taken AEDs during pregnancy and 32 (46.4%) had not. In the AED non-exposed group of 32 neonates, two babies (2.9%) had germinal matrix hemorrhage grade I diagnosed with US, one (1.4%) was SFD and one (1.4%) had feeding problems.

In the AED-exposed group of 37 neonates, nine babies (13%) had germinal matrix hemorrhage grade I, six (8.6%) were SFD, five (7.24%) had feeding problems, four (5.8%) had withdrawal symptoms and three (4.3%) "macro" congenital anomalies (Table 1).

Among neonatal problems in the group exposed to a single AED (24 neonates) we treated five cases of SFD (20.8%), five (20.8%) with germinal matrix hemorrhage grade I, two (8.3%) with "major" congenital malformations, two (8.3%) with feeding problems and one (4.1%) case of withdrawal symptoms. Most of the babies (19/24) in this group had been exposed to carbamazepine, and when these neonates were considered separately, the percentage of problems was as follows: four (21%) had germinal matrix hemorrhage grade I, three (15.7%) were SFD, two (10%) had congenital malformations and one had feeding problems (Table 2).

In the group exposed to polytherapy (13 neonates), the higher percentages of cerebral hemorrhages (30.7%), feeding problems (23.1%) and withdrawal symptoms (23.1%) were notable.

In the control non-exposed group of newborns of 211 healthy women who gave birth at the Maribor Department of Perinatology in the same period (1998–2002), we identified 23 (10.9%) newborns who were SFD, five (2.4%) cases with germinal matrix hemorrhage grade I, five (2.4%) cases with major congenital malformations and seven (3.3%) with feeding problems.

The statistical likelihood analysis (Fisher) of the incidence of congenital malformations, SFD, intracranial hemorrhage, feeding problems and withdrawal symptoms in three groups of newborns of epileptic mothers (group 1 exposed *in utero* only to the mother's epilepsy; group 2 exposed to one AED *in utero*; group 3 exposed to two or more AEDs) confirmed a significantly higher incidence of intracranial hemorrhage in the newborns exposed to AED *in utero*. The results of the analysis for congenital malformations, SFD, feeding problems and withdrawal symptoms were non-significant.

The statistical likelihood analysis (chi-squared) of the incidence of these neonatal problems in the 211 non-exposed control newborns of healthy mothers and the 69 newborns of epileptic mothers again confirmed a signifi-

Table 1. Comparison of clinical problems in 69 newborns (32 AED non-exposed, 37 exposed to AED during fetal life) of women with epilepsy and in 211 newborns of healthy mothers

	Problems in newborns					
	No. Cases	SFD	ICH	CM	FP	WS
Women with epilepsy, no AED during pregnancy	32	1 (1.4%)	2 (2.9%)		1 (1.4%)	
Women with epilepsy, AED during pregnancy	37	6 (8.6%)	9 (13%)	3 (4.3%)	5 (7.2%)	4 (4.3%)
Women with epilepsy	69	7 (10%)	11 (15.9%)	3 (4.3%)	6 (8.6%)	4 (4.3%)
Healthy women	211	23 (10.9%)	5 (2.4%)	5 (2.4%)	7 (3.3%)	0

SFD small for date; *ICH* intracranial hemorrhage; *CM* congenital malformation; *FP* feeding problems; *WS* withdrawal symptoms.

Table 2. Comparison of neonatal clinical problems in two groups differently exposed to antiepileptic drugs (mono- and polytherapy)

	Problems in neonates					
	No. cases	SFD	ICH	CM	FP	WS
Monotherapy						
Carbamazepine	19	3	4	2	1	
Primidone	1	1				
Diazepame	1					
Valproic ACID	2	1	1		1	1
Phenobarbital	1					
Total	24	5 (20.8%)	5 (20.8%)	2 (8.3%)	2 (8.3%)	1 (4.1%)
Polytherapy						
Valproic a. + Primidone	3				1	1
Valproic a. + Carbamazepine	3		2			1
Valproic a. + Lamotrigine	1					1
Bromasepane + Carbamazep	3		1	1	1	
Carbamazep + Phenobarbital	2	1	1		1	
Phenob. + Clonasepane	1					
Total	13	1 (7.6%)	4 (30.9%)	1 (7.6%)	3 (23.1%)	3 (23.1%)

SFD small for date; *ICH* intracranial hemorrhage; *CM* congenital malformation; *FP* feeding problems; *WS* withdrawal symptoms.

cantly higher incidence of intracranial hemorrhage and withdrawal symptoms in the AED-exposed group.

Discussion

Based on numerous studies [19–24], the effect of AEDs on the occurrence of malformations in neonates was defined by Volpe [18], who stated that in neonates of epileptic mothers taking AEDs during pregnancy, malformations occur in 6.5%, whereas in neonates of epileptic mothers without AED therapy they occur in 2% (2.7% in the control group). In our study, in the group of 37 newborns exposed *in utero* to AED we found major malformations in 4.3% (2.4% in the 211 control non-exposed newborns), but the results of statistical likelihood analysis (Fisher) of the incidence of congenital malformations in three groups of newborns (1/ not exposed to AEDs *in utero*; 2/ exposed to one AED *in utero*; 3/ exposed to two or more AEDs) were non-significant. We stress that in our studied group of epileptic pregnant women only 53.6% had taken antiepileptic drugs during pregnancy, and in the authors' opinion this may be a consequence of the Slovene treatment strategy during pregnancy, namely to use as few AEDs as possible at the lowest dose to maintain seizure control. We cannot ignore the fact that women with epilepsy develop a comprehensive picture of anxiety, which is frequently the cause of their fear of side effects and the discontinuation of AED therapy [25].

Some studies point out the negative effect of polytherapy with specific AEDs, particularly phenytoin (a hydantoin derivative), phenobarbitone and primidone. Data show a smaller number of malformations if the patients had taken only one AED, and only rarely one of the above-mentioned types of AED [26]. Nevertheless, the decrease in the use of AEDs brought about a 50% decrease in the incidence of malformations in the neonates. The most frequently stated congenital malformations related to maternal AED intake are congenital cardiac defect and cleft lip and/or palate [27]. Congenital cardiac defect is considered to be four times more frequent in this population of children than in others, and cleft lip and cleft palate are 10 times more frequent [28]. Morrel, Zahn and Hanson et al. describe characteristic deviations in the child's development after intrauterine exposure to AEDs [20, 21, 29]. They describe cases of exposure to phenytoin with phenobarbitone, less frequently also with primidone. The exposure to phenytoin only is called »fetal hydantoin syndrome«, its characteristics being prenatal and postnatal growth disturbances, microcephaly, retardation in development, the characteristic appearance of head and face, short neck, hypoplasia of nails and distal phalanges, among others [18]. Similar groups of signs were also described in exclusive exposure to phenobarbitone [30], primidone [31] and carbamazepine [32]. Our three discovered cases of congenital malformations in infants exposed to AEDs during pregnancy were: a case of congenital cardiac defect, a case of deformity of the skeleton and a case of chromosome anomaly. All three cases were related to carbamazepine therapy.

Presumably the mechanism of the teratogenic effect of phenytoin, phenobarbitone, primidone and carbamazepine may relate to the metabolites of these drugs. Microsome oxygenase metabolizes these drugs to epoxides, which are highly reactive oxydative metabolites that can bind to nucleic acids and impair developmental processes. These highly reactive compounds are detoxified by epoxide hydrolase by decomposition to a less harmful metabolite (dihydrodiol). A lack of epoxide hydrolase in the fetus can lead to an enhanced level of the dangerous epoxides, to which Buehler et al. ascribed a

teratogenic effect [33, 34]. Other potential mechanisms of teratogenesis induced by phenytoin and other anticonvulsants also include disturbances of folate metabolism. This mechanism could be the basis for the approximately 1% risk of neural tube defects in children of mothers treated with carbamazepine [35].

Valproic acid is also widely used as an AED and is connected with an increased risk of teratogenic effect on the central nervous system. The features of fetal valproate syndrome, apart from smaller craniofacial anomalies, are skeletal defects of the limbs and cardiac defects. The reported incidence of valproate syndrome features in the neonates of women with valproate intake during pregnancy varies from 10% to 50% [36]. The prevalent occurrence of valproic embryopathy is growth retardation in 30% [37]. In one of the most recent studies on valproate-related embryopathies [38], researchers from the Institute for Medical Genetics at the University of Helsinki describe three families with valproic embryopathy syndrome expressed in all descendants. The results call attention to congenital sensitivity to the fetotoxic effects of valproic acid. The risk of embryopathy recurring in a subsequent pregnancy is high, which should no doubt be considered in counseling procedures and treatment with AED during pregnancy.

Bleeding in the neonate is the next possible complication of maternal AED treatment, particularly with phenytoin, barbiturates, primidone and carbamazepine [39]. In our own study results, 9 out of 11 germinal matrix hemorrhages grade I were carbamazepine-related.

In order of decreasing frequency, the sites of hemorrhage are the skin, liver, gastrointestinal tract, intracranial sites and other parts, the hemorrhage appearing soon after birth. The cause lies in increased vitamin K degradation and impaired action of vitamin K on hepatic production of prothrombin. The pathogenetic mechanism by which the antiepileptic drugs lead to vitamin K deficiency may relate primarily to increased degradation of vitamin K by fetal hepatic microsomal oxydase enzymes, known to be inducible by phenytoin, phenobarbitone, primidone and carbamazepine [40].

Management of newborn infants exposed to AEDs during the fetal period should include:

– Consideration of delivery by cesarean section if a difficult or traumatic delivery is predicted,
– Administration of oral vitamin K (10 mg/day) to the mother prior to delivery during the last month of pregnancy. Parenteral vitamin K should be administered as soon as possible after the onset of labor if oral vitamin K was not given,
– Intramuscular administration of vitamin K to the infant immediately after birth [7].

Conclusion

There is no doubt that modern AEDs make it possible for epileptic women to lead a better quality of life, including a stable satisfying partnership and the need for family planning. Like any other drug, AEDs are associated with adverse effects. However, as proved by the results of our study, their effects are of less consequence than those of uncontrolled convulsive seizures, particularly if the physician has a good insight into AED pharmacodynamics and possible reactions in the mother and child.

Our study found an increased risk of subependimal hemorrhage in children of women exposed to carbamazepine. Women under treatment should be informed about the increased risk of hemorrhage and the possibility of preventive use of vitamin K in the last month of pregnancy.

References

1. Olafsson E, Hallgrimson JT, Hauser WA, Ludwigsson P, Gudmundsson G (1998) Pregnancies of women with epilepsy: a population based study in Iceland. Epilepsia 39: 887–892
2. Kallen B (1986) A register study of maternal epilepsy and delivery outcome with special reference to drug use. Acta Neurol Scand 73: 253–259
3. Sonneveld SW, Correy JF (1990) Outcome of pregnancies complicated by epilepsy in Tasmania 1981–1988. Aust NZ J Obstet Gynecol 30: 286–289
4. Russell AJC, Macpherson H, Cairnie V, Brodie MJ (1996) The care of pregnant woman with epilepsy. Seizure 5: 271–275
5. Zahn C (1998) Neurologic care of pregnant women with epilepsy. Epilepsia 39 [Suppl 8]: S26–S31
6. Sabers A, A Rogvi-Hansen B, Dam M, et al (1998) Pregnancy and epilepsy. A retrospective study of 151 pregnancies. Acta Neurol Scand 97: 164–170
7. Ried S, Beck-Mannagetta G (1996) Epilepsy, pregnancy and child. Blackwell Science. Berlin Vienna
8. Jick SS, Terris BZ (1997) Anticonvulsants and congenital malformations. Pharmacotherapy 17: 561–564
9. Bertollini R, Mastroiacovo P, Segni G (1985) Maternal epilepsy and birth defects. A case control study in the Italian Multicentric Registry of birth defects. Eur J Epidemiol 1: 67–72
10. Kaneko S, Battino D, Andermann E, et al (1999) Congenital malformations due to antiepileptic drugs. Epilepsy Res 33: 145–158
11. Omtzigt JG, Los FJ, Hagenaars AM, Stewart PA, Sahs ES, Lindhout D (1992) Prenatal diagnosis of spina bifida aperta after first trimester valproate exposure. Prenat Diagn 12: 893–897
12. Lindhout D, Omtzigt JG (1994) Teratogenic effects of antiepileptic drugs. Implications for the management of epilepsy in women of childbearing age. Epilepsia 35 [Suppl 4]: S 19–28
13. Battino D, Granata T, Binelli S, et al (1992) Intrauterine growth in the offspring of epileptic mothers. Acta Neurol Scand 86: 555–557
14. Steegers-Theunissen RP, Renier WO, Borm GF, et al (1994) Factors influencing the risk of abnormal pregnancy outcome in epileptic women: a multi centre prospective study. Epilepsia Res 18: 261–269
15. Sawhney H, Vasishta K, Suri V Khunnu B, Goel P, Sawhney IM (1996) Pregnancy with epilepsy – a retrospective analysis. Int J Gynecol Obstet 54: 17–22
16. Ornoy A, Cohen E (1996) Outcome of children born to epileptic mothers treated with carbamazepine during pregnancy. Arch Dis Child 75: 517–520
17. Dessens AB, Cohen-Kettenis PT, Mellenbergh GJ, Koppe JG, et al (2000) Association of prenatal phenobarbital and phenitoin exposure with small head size at birth and with learning problems. Acta Pediatr 89: 533–541

18. Volpe JJ (2000) Neurology of the newborn, 4th edn. WB Saunders, Philadelphia
19. Speidel BD, Meadow SR (1972) Maternal epilepsy and abnormalities of the fetus and newborn. Lancet 2: 839
20. Morrell MJ (1998) Guidelines for the care of women with epilepsy. Neurology 51: S21–S27
21. Zahn CA, Morrell MJ, Collins SD, et al (1998) Management issues for women with epilepsy: a review of the literature. Neurology 51: 949–956
22. Kaneko S, Battino D, Andermann E, et al (1999) Congenital malformations due to antiepileptic drugs. Epilepsy Res 33: 145–158
23. Wide K, Winbladh B, Tomson T, et al (2000) Psychomotor development and minor anomalies in children exposed to antiepileptic drugs in utero: a prospective population based study. Dev Med Child Neurol 42: 87–92
24. Fonager K, Larsen H, Pedersen L, Sorensen HT (2000) Birth outcomes in women exposed to anticovulsant drugs. Acta Neurol Scand 101: 289–294
25. Devinsky O (1996) Quality of life with epilepsy. In: Willie E (ed) The treatment of epilepsy, 2nd edn. Williams and Williams, Baltimore, pp 1145–1150
26. Lindhout D, Meinardi H, Meier JW, Nau H (1992) Antiepileptic drugs and teratogenesis in two consecutive cohorts. Changes in prescription policy paralleled by changes in pattern of malformations. Neurology 42: 94–110
27. Paulson GW, Paulson RB (1981) Teratogenic effects of anticonvulsants. Arch Neurol 38: 140
28. Oguni M, Dansky L, Andermann E, et al (1992) Improved pregnancy outcome in epileptic women in the last decade. The relationship to maternal anticonvulsant therapy. Brain Dev 14: 371–380
29. Hanson JW, Smith DW (1975) The fetal hydantoin syndrome. J Pediatr 87: 285
30. Seip M (1976) Growth retardation, dysmorphic facies and minor malformations following massive exposure to phenobarbitone in utero. Acta Pediatr Scand 65: 617
31. Hoyme HE, Clericuzio CL (1985) Fetal primidone effects. Pediatr Res 19: 326A
32. Vestermark V, Vestermark S (1991) Teratogenic effect of carbamazepine. Arch Dis Child 66: 641–642
33. Buehler BA, Delimont D, Van Waes M, Finell RH (1990) Prenatal prediction of fetal hydantoin syndrome. N Engl J Med 322: 1567–1572
34. Finell RH, Buehler BA, Kerr BM, et al (1992) Clinical and experimental studies linking oxidative metabolism to phenitoin induced teratogenesis. Neurology 42: 25–31
35. Dansky LV, Rosenblatt DS, Andermann E (1992) Mechanisms of teratogenesis: folic acid and antiepileptic therapy. Neurology 42: 32–42
36. Thisted E, Ebbesen F (1993) Malformations after exposure to valproate in utero. Arch Dis Child 69: 288–291
37. Kozma C (2001) Valproic acid embriopathy. Am J Med Genet 98: 168–175
38. Malm H, Kajantie E, Kivirikko S, Kaariainen H, Peippo M, Somer M (2002) Valproate embryopathy in three sets of siblings: further proof of hereditary susceptibility. Neurology 59: 630–632
39. Renzulli P, Tuchschmid P, Eich G, et al (1998) Early Vit K deficiency bleeding after maternal Phenobarbital intake. Eur J Pediatr 157: 663–665
40. Cornelissen M, Steegerstheunissen R, Kollee L, et al (1993) Increased incidence of neonatal vitamin K deficiency resulting from maternal anticonvulsant therapy. Am J Obstet Gynecol 16: 923–928

Correspondence: Silva Burja, M.D., Ph.D., Maribor Teaching Hospital, Department of Gynecology and Perinatology, Ljubljanska 5, 2000 Maribor, Slovenia,
E-mail: silva.burja@guest.arnes.si