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Maternal Use of Antiepileptic Drugs and the Risk of Major Congenital Malformations: A Joint European Prospective Study of Human Teratogenesis Associated with Maternal Epilepsy

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Summary: *Purpose:* To quantify the risks of intrauterine antiepileptic drug (AED) exposure in monotherapy and polytherapy.

Methods: Data from five prospective European studies totaling 1,379 children were pooled and reanalyzed. Data were available for 1,221 children exposed to AED during pregnancy and for 158 children of unexposed control pregnancies.

Results: Overall, when comparing a subgroup of 192 children exposed to AED with 158 children of matched nonepileptic controls, there was an increased risk of major congenital malformations (MCA) in children exposed to AED during gestation [relative risk (RR) 2.3; 95% confidence interval (CI): 1.2–4.7]. A significant increase in risk was found for children exposed to valproate (VPA) (RR 4.9; 95% CI: 1.6–15.0) or carbamazepine (CBZ) (RR 4.9; 95% CI: 1.3–18.0) in monotherapy. When comparing different AED regimens during all 1,221 pregnancies, risks of MCA were significantly increased for the combination of phenobarbital (PB) and ethosuximide (RR 9.8; 95% CI: 1.4–67.3) and the combination of phenytoin, PB, CBZ, and VPA (RR 11.0; 95% CI: 2.1–57.6). Offspring of mothers using >1,000 mg VPA/day were at a significantly increased risk of MCA, especially neural tube defects, compared to offspring exposed ≤600 mg VPA/day (RR 6.8; 95% CI: 1.4–32.7). No difference in risk of MCA was found between the offspring exposed to 601–1,000 mg/day and ≤600 mg/day.

Conclusions: This reanalysis shows that VPA is consistently associated with an increased risk of MCA in babies born to mothers with epilepsy. Significant associations were also observed with CBZ. Larger prospective population-based studies are needed to evaluate the risks of many other less frequently prescribed treatment regimens, including newly marketed AEDs. **Key Words:** Antiepileptic drugs—Major congenital malformations—Pregnancy—Epileptic offspring.

Maternal use of antiepileptic drugs (AEDs) during pregnancy has been associated with an increased risk of major congenital abnormalities (MCA) in the fetus. Yet in many women planning a pregnancy antiepileptic drugs cannot be discontinued because of the risk of seizures during pregnancy, which can be harmful to both mother and child (1–3). Furthermore, acute discontinuation during early pregnancy is also not recommended because of the risk of increased numbers of seizures and status epilepticus (4–6). Many children of women with epilepsy are therefore at a two- to threefold increased risk of congenital malformations as compared with the general population (7–14) and an important clinical issue is how to treat women with epilepsy during pregnancy (15–18).

Many questions concerning risks associated with the specific AEDs are unanswered. In the studies conducted to date, no specific drug regimen has consistently shown a lower risk than any other, suggesting that AED therapy is implicitly related to an increased risk of congenital malformations. However, in most of these studies, the number of pregnancies was relatively small (19–23), which limits the possibilities for detecting potential

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dose–response relationships. Furthermore, studies may differ in regard to both definitions and procedures. In a collaborative analysis, these factors can be taken into account by increasing the number of subjects, application of standardized definitions, and evaluation of effects that are consistent across studies.

Therefore, to quantify the specific risks of AEDs in monotherapy and polytherapy, we reanalyzed data pooled from five prospective European studies. The present study focuses on pregnancies in women with epilepsy treated with AEDs. The first aim was to assess the risk of MCA of children exposed in utero to AEDs during pregnancy as compared with the risk of children not exposed to AEDs. The second aim was to quantify risks of MCA associated with specific AED regimens.

METHODS

For the present study, raw data from five studies were pooled. These studies included were prospective studies conducted in Europe from 1971 to 1990. The studies were selected on the basis of their prospective design and before knowing the outcome to minimize selection bias. One study was conducted in Helsinki, Finland; 2 studies were conducted in Germany, 1 in Berlin (former West Berlin) and 1 in Magdeburg; and 2 were conducted in The Netherlands, 1 in the South West Netherlands, including, the municipality of Rotterdam, and 1 in the outpatient clinics of the Dutch Special Centres for Epilepsy. Included in the studies were 896 women with epilepsy treated with AEDs and 1,221 children born to these subjects, and 158 children born to nonepileptic control subjects (Table 1). Of the AED-treated women, 326 (36%) had generalized epilepsy, 484 (54%) had localization-related epilepsy, and 28 (3%) had unclassified epilepsy; in 58 (7%) women, the type of epilepsy was unknown. The assessment of seizures during pregnancy, especially in the first trimester, was incomplete and varied among study groups with respect to assessment procedures and definition. Therefore, adequate and comparable data on seizure frequency were not available for reanalysis.

Individual studies

During the 1981 workshop in Berlin on Epilepsy, Pregnancy, and the Child, participating groups compared their prospective study designs and concluded that the different studies were adequately comparable and therefore suitable for a collaborative analysis, once the individual studies had been published. All were designed as prospective studies of the reproductive outcome of preg-

TABLE 1. *Details of individual studies*

Parameter	Germany		Finland, Helsinki	Netherlands	
	Berlin	Magdeburg		Rotterdam	Epilepsy Institutes
Years of study	1979–1990	1979–1987	1976–1979	1985–1990	1972–1990
No. of AED-exposed pregnancies	150	42	106	305	618
No. of nonepileptic pregnancies	116	42	—	—	—
Matching criteria	Maternal age, parity, social class, smoking, abortions	Maternal age, parity, social class, smoking, abortions, sex, obstetric clinic	—	—	—
Time of matching	During pregnancy	After delivery	—	—	—
Exclusion criteria	Immature delivery	Stillbirth and neonatal deaths, nonepileptic controls with family history of epilepsy	Immature delivery	—	—
Endpoints	Major and minor congenital malformations and body measurements	Major and minor congenital malformations and body measurements	Major and minor congenital malformations and body measurements	Major congenital malformations and body measurements	Major congenital malformations and body measurements
Time of examination	Birth, 1 and 4 yr	Birth, 1.5 and 5 yr	Birth, 1.5 and 5.5 yr	0–3 mo	0–3 mo
Examination by	Pediatrician	Pediatrician	Pediatric neurologist	Gynecologist or pediatrician	Gynecologist or pediatrician
Diagnosis of epilepsy by	Neurologist	Neurologist	Neurologist	Neurologist	Neurologist
No. of mothers exposed to AEDs	123	32	97	261	411
No. of mothers nonepileptic	116	42	—	—	—
Exposure information	Prospective	Prospective	Prospective	Prospective	Prospective

AED, antiepileptic drug.

nancies of women with epilepsy. The studies recruited all consecutive pregnant women with epilepsy. These studies conducted in Berlin and Magdeburg also included nonepileptic control pregnancies. During the 1985 International Epilepsy Symposium held in Hamburg, Germany, a collaborative analysis of the data from these centers was agreed upon and a grant application was approved by the International League Against Epilepsy and forwarded to the Klingenstein foundation. The comparability of case ascertainment and the assessment of MCA in the individual studies were evaluated in visits to the study centers and discussions of the individual protocols. The study design, in particular the selection of the exposed and nonexposed pregnancies used in this analysis, is described individually for each study herein. The studies are ordered alphabetically by city and country.

Berlin, Germany

The Berlin study was conducted between 1979 and 1990 (24). The study comprised 123 mothers with epilepsy. Included were 150 AED-exposed pregnancies (Table 1). Only patients whose epilepsy diagnosis was confirmed by a neurologist and in whom the first seizure occurred before pregnancy were included. Of the cohort, 80% were ascertained through 12 obstetric clinics in the area of Berlin and 20% was ascertained through the neurology department at the former University Hospital Charlottenburg. Control pregnancies (n = 116) were selected through the obstetric clinics, matched for maternal age at delivery, parity, social class, smoking habits, and previous abortions. Patients and controls were recruited during pregnancy before fetal outcome was known. For each pregnancy, data on maternal epilepsy and AED therapy, family history, obstetric history, and smoking, alcohol, and drug abuse were collected. Stillbirths and neonatal deaths were included. At birth and at 1 and 4 years, children underwent physical examination by a pediatrician according to a standardized protocol. The endpoints for examination were major and minor malformations, including body measurements, occurrence of neural tube defects, cleft lip and palate, skeletal malformations, abdominal defects, genitourinary defects, cardiac defects, and dysmorphic features.

Helsinki, Finland

The Helsinki study was conducted based on ascertainment of pregnancies between 1976 and 1979 (25) and comprised 97 mothers with epilepsy. Included were 106 AED-exposed pregnancies (Table 1). Only patients in whom the epilepsy diagnosis was confirmed by a neurologist and in whom the first seizure occurred before pregnancy were included. Subjects were recruited during weeks 7–24 of pregnancy; all maternity units were asked to refer patients with epilepsy for the study to the Helsinki University City Hospital. Patients with premature deliveries (pregnancy duration 16–24 weeks) were excluded, but stillbirths/neonatal deaths were not. Data from control pregnancies were not available for this reanalysis. For each pregnancy, data on maternal epilepsy and AED treatment, family history, obstetric history, and smoking habits were collected. At birth and at 1.5 and 5.5 years of age, each child was examined by a pediatric neurologist according to a standardized protocol (26). The endpoints for examination were major and minor malformation, including body measurements, occurrence of neural tube defects, cleft lip and palate, skeletal malformations, abdominal defects, genitourinary defects, cardiac defects, and dysmorphic features.

Magdeburg, Germany

Pregnancies were ascertained between 1979 and 1987 according to a protocol similar to that of the Berlin study (27,28). There were 32 mothers with epilepsy and 42 AED-exposed pregnancies (Table 1). The diagnosis of epilepsy was always confirmed by a neurologist. In all but 4 patients, the first seizure occurred before pregnancy. Patients were referred to the coordinating pediatric neurologist by two obstetric departments. The next delivery after birth of the exposed infant was selected as a control pregnancy (n = 42). The matching criteria were sex, obstetric clinic, maternal age at delivery, parity, social class, smoking habits, and previous abortions. Women with a positive family history of epilepsy were excluded as controls. Subjects were recruited during pregnancy. Patients and controls with stillbirths and neonatal deaths were excluded, since the primary endpoint of the study was postnatal development. Data on maternal epilepsy and AED therapy, family history, obstetric history, and smoking, alcohol, and drug abuse were collected. At birth and at 1.5 and 5 years, physical examination was performed by a pediatrician according to a standardized protocol. The endpoints for examination were major and minor malformations, including body measurements, occurrence of neural tube defects, cleft lip and palate, skeletal malformations, abdominal defects, genitourinary defects, cardiac defects, and dysmorphic features.

Rotterdam, The Netherlands

The Rotterdam study was conducted from 1985 to 1990 and comprised 261 women with epilepsy (23,29–31) consecutively referred to the outpatient clinic for prenatal diagnosis of the University Hospital Rotterdam, because of epilepsy with AED (or without AED) treatment. Subjects were recruited before month 4 of pregnancy. Only patients whose epilepsy diagnosis was confirmed by a neurologist were included. Data were available on 305 AED-exposed pregnancies (Table 1). Either amniocentesis or structural ultrasound (and in most patients, both) was performed. Some pregnancies were interrupted because of MCA discovered during prenatal testing. These pregnancies were included in the study.

No control pregnancies are available. Data on maternal epilepsy and AED therapy, family history, obstetric history, and smoking, alcohol, and drug abuse were collected. Pregnancies ending in stillbirth or neonatal death were included. Neonatal examination was performed by a gynecologist or pediatrician, and defects observed in the first 3 months of life were included. The main endpoints were MCA, including body measurements, occurrence of neural tube defects, cleft lip and palate, skeletal malformations, abdominal defects, genitourinary defects, cardiac defects, and dysmorphic features.

Institutes of Epilepsy, The Netherlands

The Institutes of Epilepsy cohort consisted of 411 women with epilepsy derived from 1 of 14 outpatient clinics of the Special Centres for Epilepsy in The Netherlands (Instituut voor Epilepsie bestrijding Heemstede, Kempenhaeghe Heeze, and Dr. Hans Berger-kliniek Breda) from period 1972 to 1990. In these centers, ~7% of all patients with epilepsy in the Netherlands are treated. Included were 618 consecutive AED-exposed pregnancies (Table 1). The entire cohort was subdivided into three groups (A, B, and C). The first study (cohort A) was conducted between 1972 and 1979 and comprised 151 AED-exposed pregnancies (32–34). The second study (cohort B) was conducted between 1980 and 1985 and comprises 172 AED-exposed pregnancies (11). The remaining pregnancies (cohort C) were collected between 1985 and 1990 and consist of 295 AED-exposed pregnancies (not previously published). Diagnosis of epilepsy was confirmed by a neurologist. No control pregnancies are available. Subjects were recruited during or before pregnancy, and AED exposure was monitored during pregnancy. All abortions, premature deliveries, and stillbirths are included. Data on maternal epilepsy and AED treatment, family history, obstetric history, and smoking, alcohol, and drug abuse were collected by the attending neurologist, and forms were completed at the first visit to the outpatient clinic after delivery (usually 3–5 months after delivery). The neonatal examination was performed by a gynecologist or pediatrician, and MCA discovered within 3 months after birth were used in the analysis. The main endpoints were MCA, including body measurements, occurrence of neural tube defects, cleft lip and palate, skeletal malformations, abdominal defects, genitourinary defects, cardiac defects, and dysmorphic features.

Assessment of malformations

For this analysis, we defined MCA as an abnormality of an essential embryonal structure, present at birth or discovered during the first 3 months of life and requiring major intervention before the first year of life. Examples of MCA according to this definition are: neural tube defects, congenital heart defects, hypospadias, cleft lip and palate, pre- and/or postaxial polydactyly, club foot, congenital hip dysplasia requiring plaster therapy, and inguinal hernia, requiring operation.

Data analysis

Raw data from the participating sites were pooled and reanalyzed for the reanalysis. The data were analyzed in two ways. First, the occurrence of MCA associated with maternal epilepsy and AED exposure were compared with the occurrence of MCA in control pregnancies. Because the latter were available only for the Berlin and Magdeburg studies, this analysis was limited to those two studies. We performed multiple logistic regression to estimate the relative risk (RR), using all nonepileptic controls as a reference and adjusting for the matching variables by including them in the regression model. RR are presented with a 95% confidence interval (95% CI), which will exclude the value 1 in case of statistical significance ($p < 0.05$).

Second, risks associated with specific AED regimens were compared between pregnancies exposed to different regimens. RR were used to quantify the strength of the association and are presented with 95% CI. Multiple logistic regression analysis was used to adjust for putative confounding variables such as maternal age, parity, social class, sex of the child, study site, type of epilepsy, and dose of medication. If AEDs were used in sufficient numbers, we tested for the presence of a dose–response relationship, with cutoff points based on tertiles. For this analysis, no data from the Helsinki study were available.

RESULTS

There were differences among the five studies with regard to age at birth, parity, social class, and sex of the child (Table 2). Pregnancies occurred at younger age in Germany and at older age in the Rotterdam study. There were more nulliparous women in the Dutch Epilepsy Institutes and in Germany. There were fewer skilled manual laborers in the Rotterdam study.

The distribution of the different AED regimens for each center, with the percentages of MCA for each regimen, is shown in Table 3. Prescription regimens differed between the centers. In the Rotterdam study and the Dutch Institutes of Epilepsy study, there was a tendency toward more frequent prescription of carbamazepine (CBZ), valproate (VPA), and combination therapies, whereas phenytoin (PHT) and phenobarbital (PB) were prescribed less frequently than in the other studies. In Berlin and Magdeburg, PHT and primidone (PRM) were prescribed more often than CBZ and VPA. In Helsinki, the most frequently prescribed drugs were PHT and CBZ. The risk of MCA also differed significantly among centers. Significantly more MCA were detected in Berlin (16%) and Magdeburg (14%) than in the other centers (Table 3).

We first compared the risks of MCA in AED-exposed

TABLE 2. *Details of study population*

Parameter	Germany: Berlin and Magdeburg[a]		Finland, Helsinki	Netherlands	
	AED-exposed	Nonepileptic controls		Rotterdam	Epilepsy Institutes
No. of pregnancies	192	158	106	305	618
Age (yr), n (%)					
<19	18 (9)	11 (7)	4 (4)	8 (2)	5 (1)
20–24	72 (38)	64 (41)	28 (26)	60 (20)	137 (22)
25–29	68 (35)	51 (32)	45 (42)	103 (34)	297 (48)
30–34	28 (15)	25 (16)	20 (19)	97 (32)	146 (24)
35+	6 (3)	7 (4)	9 (9)	37 (12)	33 (5)
Parity, n (%)					
0	82 (42)	72 (46)	—	121 (40)	311 (50)
1	57 (30)	59 (37)	—	108 (35)	210 (34)
2+	52 (27)	26 (16)	—	74 (24)	97 (16)
Unknown	1 (1)	1 (1)	—	2 (1)	—
Social class, n (%)					
Academic degree	3 (2)	3 (2)	15 (14)	17 (6)	—
White collar	41 (21)	29 (19)	33 (31)	102 (33)	—
Skilled manual	104 (54)	106 (67)	45 (43)	88 (29)	—
Unskilled manual	39 (20)	18 (11)	13 (12)	37 (12)	—
Unknown	5 (3)	2 (1)		61 (20)	—
Sex of child, n (%)					
M	103 (54)	84 (53)	52 (49)	148 (48)	299 (48)
F	89 (46)	74 (47)	54 (51)	156 (51)	279 (45)
Unknown[b]	—	—	—	1 (0.3)	40 (7)

AED, antiepileptic drug.

[a] In all, 150 exposed and 116 nonexposed pregnancies were derived from Berlin; 42 exposed and 42 nonexposed pregnancies were derived from Magdeburg.

[b] Miscarriage; no sex determination.

pregnancies with those in matched control pregnancies, using the data from the studies from Berlin and Magdeburg (Table 4). Overall, we noted a significantly increased risk of MCA in children of mothers with epilepsy treated with AEDs during pregnancy as compared with children of healthy controls (RR 2.3, 95% CI 1.2–4.7). Moreover, the risk of MCA was significantly increased in children of women treated with CBZ (RR 4.9, 95% CI 1.3–18.0) and in children exposed to VPA (RR 4.9, 95% CI 1.6–15.0). Most other therapies also showed an increased RR, although it was not significant. However, the number of women treated with these AEDs was very small, in particular the number treated with PB and with most polytherapy regimens. When adjustment was made for maternal age, sex of the child, social class or parity of the mother, or type of maternal epilepsy in our multiple logistic regression analysis, none of the RR shown in Table 4 changed materially (data not shown in Table 4).

Second, using the data of all centers, we compared the risks of MCA between the different drug regimens. We first calculated the risk of MCA in the different AED regimens, using all AED-exposed pregnancies pooled from all five centers (Table 5). The AED (monotherapy) associated with the lowest percentage of MCA (i.e., PHT) was used as a reference for comparisons with other AED regimens. In the crude overall analysis, there were no significant differences in RR of MCA between the different monotherapy AED regimens. In children of mothers treated with VPA monotherapy, however, the absolute risk of neural tube defects was 3.8% as compared with 1.0% in those receiving CBZ monotherapy and 0% in those receiving other monotherapy regimens. For the polytherapies studied, only the combinations of PB and ethosuximide (ESM) (RR 9.8, 95% CI 1.4–67.3; n = 5) and PHT, PB, CBZ, and VPA (RR 11.0, 95% CI 2.1–57.6; n = 7) were shown to pose a significantly increased risk of MCA as compared with PHT monotherapy, but very few women received these drug combinations. When adjustment was made for confounders such as type of epilepsy (Table 5), study center, and socioeconomic status, only study center influenced the effects of the drug regimens (data not shown in Table 5). When adjustment was made for study center, the risks of MCA for the offspring of women treated with VPA (RR 3.7, 95% CI 1.2–11.8), CBZ (RR 2.8, 95% CI 1.1–7.3), and PB (RR 4.2, 95% CI 1.0–18.6) monotherapy were significantly increased. An increased risk of MCA in offspring of women treated with VPA was evident in all but the Helsinki study, in which VPA was not prescribed in monotherapy. For the other AED regimens, there was no evidence of confounding by study center. We did not find significant evidence of an association between any type of epilepsy and the risk of MCA in the offspring.

Finally, we evaluated the possibility of a dose-dependent association (Fig. 1). Due to the small catego-

TABLE 3. *Drug regimens and occurrence of MCA in AED-exposed pregnancies in different study centers*[a]

AED	Germany		Finland, Helsinki	Netherlands		Total, n (%)
	Berlin	Magdeburg		Rotterdam	Epilepsy Institutes	
CBZ	3/10 (30)	1/4 (25)	2/18 (11)	5/115 (4)	11/133 (8)	22/280 (8)
ESM	1/2 (50)	—	—	0/2 (0)	0/9 (0)	1/13 (8)
PB	0/5 (0)	1/1 (100)	—	3/18 (17)	1/24 (4)	5/48 (10)
PHT	4/28 (14)	1/5 (20)	4/46 (9)	0/29 (0)	0/33 (0)	9/141 (6)
PRM	2/27 (10)	1/12 (8)	0/1 (0)	—	1/3 (33)	4/43 (9)
VPA	4/16 (25)	2/5 (40)	—	7/64 (11)	3/99 (3)	16/184 (9)
CBZ + CZP	0/2 (0)	—	—	2/7 (29)	0/2 (0)	2/11 (18)
CBZ + VPA	—	—	1/1 (100)	2/13 (15)	6/65 (9)	9/79 (11)
PHT + CBZ	1/2 (50)	—	1/9 (11)	0/6 (0)	2/27 (7)	4/44 (9)
PHT + PB	2/15 (13)	—	2/10 (20)	1/7 (14)	0/8 (0)	5/40 (13)
PHT + VPA	1/2 (50)	0/1 (0)	0/5 (0)	0/2 (0)	1/8 (13)	2/18 (11)
PB + CBZ	—	—	0/1 (0)	0/10 (0)	1/16 (6)	1/27 (4)
PB + ESM	1/3 (33)	—	—	—	1/2 (50)	2/5 (40)
PB + VPA	1/2 (50)	—	—	0/5 (0)	2/9 (22)	3/16 (19)
PRM + VPA	1/8 (13)	0/5 (0)	—	—	—	1/13 (8)
VPA + CZP	—	—	—	0/3 (0)	1/3 (33)	1/6 (17)
VPA + ESM	1/2 (50)	—	—	0/3 (0)	2/34 (6)	3/39 (8)
CBZ + VPA + CZP	—	—	—	0/1 (0)	1/4 (25)	1/5 (20)
PHT + PB + CBZ + VPA	—	—	—	—	3/7 (43)	3/7 (43)
Others	3/26 (12)	0/9 (0)	0/15 (0)	2/20 (10)	8/132 (6)	13/202 (6)
Total	25/150 (17)	6/42 (14)	10/106 (9)	22/305 (7)	46/618 (7)	108/1,221 (9)

MCA, major congenital abnormalities; AED, antiepileptic drug; CBZ, carbamazepine; ESM, ethosuximide; PB, phenobarbital; PHT, phenytoin; PRM, primidone; VPA, valproate; CZP, clonazepam.

[a] Numbers are malformed/total exposed.

ries, we did not adjust these analyses for study center, maternal age, sex of the child, social class, parity of the mother, or maternal epilepsy. Among women treated with VPA offspring of women receiving VPA >1,000 mg/day had a significant increase in risk of MCA as compared with those of women receiving <600 mg/day (RR 6.8, 95% CI 1.4–32.7). The MCA detected in the offspring of women receiving VPA ⩾1,000 mg/day were spina bifida with or without hydrocephalus (n = 5; 28%); ventricular septal defect (n = 1, 6%); tetralogy of Fallot (n = 1, 6%); atrial septal defect (n = 1, 6%); craniosynostosis (n = 1, 6%); a combination of meningomyelocele, microcephaly, and inguinal hernia (n = 1, 6%); and a combination of aplasia of the first rib and hypersegmentation of the manubrium sterni (n = 1, 6%). PB monotherapy also showed a trend for increased risk of MCA with increasing dose, but the differences were not significant. Malformations occurring twice or more are summarized in Tables 6 and 7.

DISCUSSION

Our findings show an overall increased risk of MCA in children of mothers with epilepsy treated with AEDs during pregnancy as compared with children of healthy controls. The most pronounced increase in risk was that for children exposed in utero to VPA or CBZ monotherapy. Comparison of different AED regimens received during pregnancy showed that risk of MCA was significantly increased for the rare combination of PB and ESM and the combination of PHT, PB, CBZ, and VPA. In an analysis adjusted for study center, this risk was also significantly increased for CBZ, PB, and VPA in monotherapy. The risk associated with VPA monotherapy appeared to be dose dependent. The offspring of mothers treated with >1,000 mg/day VPA are at increased risk, in particular of neural tube defects. The risk associated with PB also appeared to be dose dependent.

Because our findings are based on nonrandomized studies, biases may have occurred. In none of the studies pooled were pediatricians or other investigators assessing the presence of MCA blinded to the exposure status of the offspring. Furthermore, in this reanalysis, the data were pooled from studies that differed considerably in

TABLE 4. *RR of MCA: Comparison of AED-exposed and nonepileptic controls*[a]

Exposures	Pregnancies, n (%)[b]	RR	95% CI
Nonepileptic controls	12/158 (8)	1.0	Reference
CBZ	4/14 (29)	4.9	1.3–18.0
PB	1/6 (17)	2.4	0.3–23.0
PHT	5/33 (15)	2.2	0.7–6.7
PRM	3/39 (8)	1.0	0.3–3.8
VPA	6/21 (29)	4.9	1.6–15.0
PHT + PB	2/15 (13)	1.8	0.4–9.4
PRM + VPA	1/13 (8)	1.0	0.1–8.6
Others	8/51 (16)	2.1	0.8–5.4

RR, relative risk; CI, confidence interval; other abbreviations as in Table 3.

[a] Data available only in Berlin and Magdeburg studies.

[b] Numbers are malformations/total exposed.

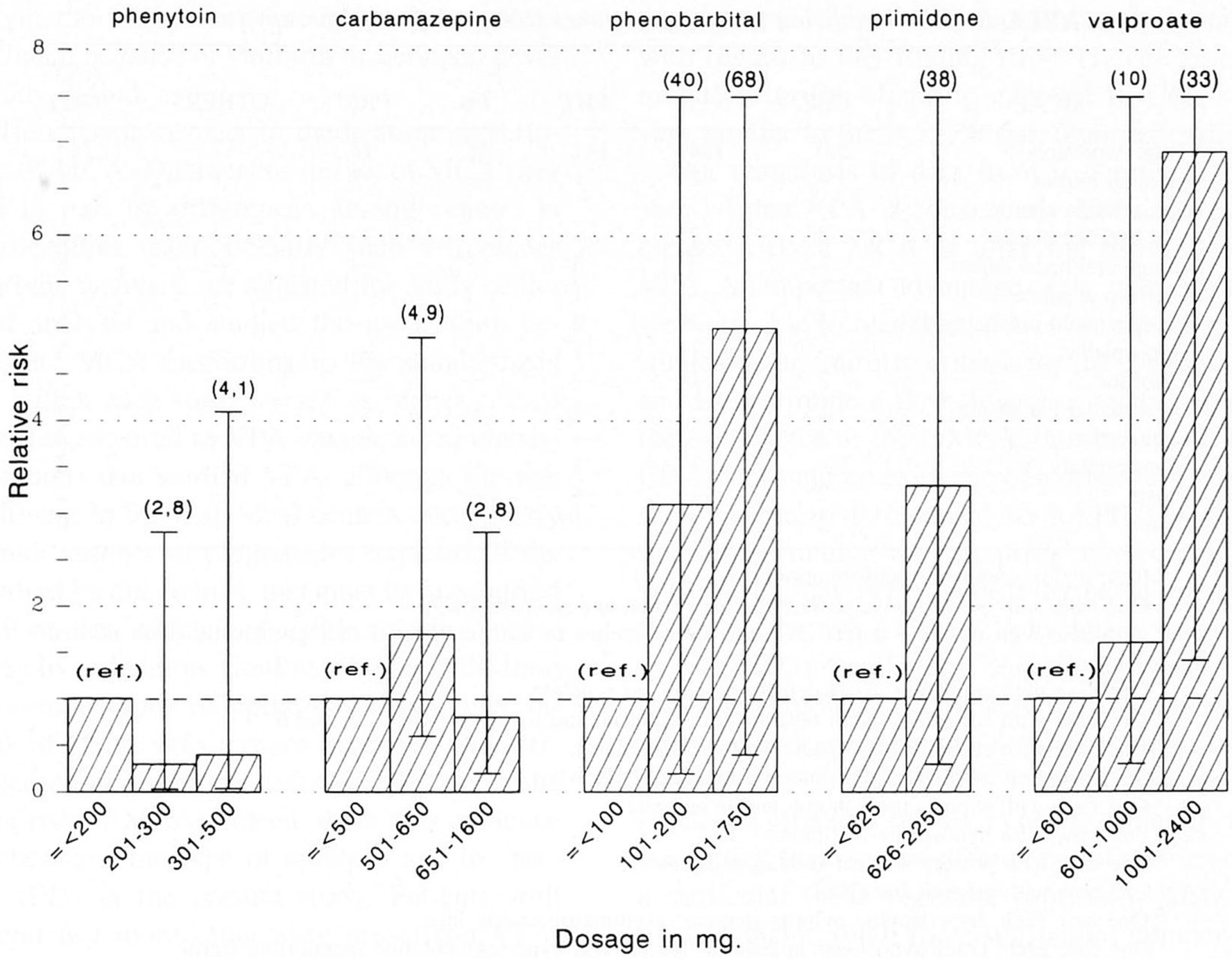

FIG. 1. Risk of major congenital malformations posed by increasing dose of the antiepileptic drug (AED) regimen in monotherapy (cutoff points at 33.3 and 66.6%). Above the columns, the upper limit for the 95% confidence interval is shown. Included are all AED regimens used in ⩾30 pregnancies.

TABLE 5. *All centers: RR of MCA, comparison of different AED regimens*

Exposures[a]	n, all centers (%)	RR (crude)	95% CI	RR (adjusted[b])	95% CI	n (first pregnancies)	RR (first pregnancies)	95% CI
PHT	9/141 (6)	1.0	Reference	1.0	Reference	8/118	1.0	Reference
CBZ[c]	22/280 (8)	1.3	0.6–2.8	1.2	0.5–2.7	17/210	1.2	0.5–2.9
ESM	1/13 (8)	1.2	0.1–10.7	0.6	0.1–6.8	0/9	—	—
PB[d]	5/48 (10)	1.7	0.5–5.4	1.9	0.5–6.9	5/37	2.2	0.7–7.1
PRM	4/43 (9)	1.5	0.4–5.2	1.0	0.3–4.0	4/32	2.0	0.6–7.1
VPA[e]	16/184 (9)	1.4	0.6–3.3	1.5	0.6–4.0	10/121	1.2	0.5–3.3
CBZ + CZP	2/11 (18)	3.3	0.6–17.6	3.6	0.6–19.7	1/5	3.4	0.3–35.3
VPA + CBZ	9/79 (11)	1.9	0.7–5.0	1.9	0.7–5.0	5/48	1.6	0.5–5.2
PHT + CBZ	4/44 (9)	1.5	0.4–5.1	1.5	0.4–5.2	4/34	1.8	0.5–6.6
PHT + PB	5/40 (13)	2.1	0.7–6.7	2.0	0.6–6.5	5/34	2.4	0.7–7.9
PHT + VPA	2/18 (11)	1.8	0.4–9.4	1.6	0.3–8.4	1/14	1.1	0.1–9.3
PB + CBZ	1/27 (4)	0.6	0.1–4.7	0.5	0.1–3.9	1/19	0.8	0.1–6.6
PB + ESM	2/5 (40)	9.8	1.4–67.3	7.5	1.0–56.0	1/3	6.9	0.6–86.4
PB + VPA	3/16 (19)	3.4	0.8–14.2	2.4	0.5–12.2	3/13	4.1	0.9–18.3
PRM + VPA	1/13 (8)	1.2	0.1–10.7	0.8	0.1–7.4	1/9	1.7	0.2–15.8
VPA + CZP	1/6 (17)	2.9	0.3–28.4	2.5	0.2–25.2	1/6	2.8	0.3–27.1
VPA + ESM	3/39 (8)	1.2	0.3–4.8	0.6	0.1–3.2	3/27	1.7	0.4–7.0
CBZ + VPA + CZP	1/5 (20)	3.7	0.4–37.0	3.7	0.4–37.6	1/2	13.8	0.8–248.0
PHT + PB + CBZ + VPA	3/7 (43)	11.0	2.1–57.6	13.8	2.5–76.9	2/6	6.9	1.1–44.2
Others[f]	13/202 (6)	1.0	0.4–2.4	0.9	0.4–2.3	13/149	1.3	0.5–2.2

Abbreviations as in Tables 3 and 4.

[a] RR calculation after adjustment for center was limited by too small numbers, except for CBZ, PB, and VPA.

[b] Adjusted for type of epilepsy.

[c] RR for CBZ adjusted for center: 2.8 (1.1–7.3).

[d] RR for PB adjusted for center: 4.2 (1.0–18.6).

[e] RR for VPA adjusted for center: 3.7 (1.2–11.8).

[f] All regimens consisting of four pregnancies or fewer.

TABLE 6. *MCA occurring two or more times with use of monotherapy (n ⩾ 20)*

MCA	CBZ	VPA	PHT	PB	PRM	OTHERS	ANY (⩾2)
Total exposures	280	184	141	48	43	17	713
Inguinal hernia	4	2[a]	1	—	3	1	11
Spina bifida aperta ± hydrocephalus	3[b]	7[a]	—	—	—	—	—
Congenital heart defect	—	2	3[c]	3[d]	—	—	8
Cleft lip ± palate	3[e]	—	1[c]	2	1	—	7
Pre-/postaxial polydactyly	3[f]	2[g]	2	—	—	—	6
Hypospadias	3[e,h]	1	1	—	—	—	5
Clubfoot	2	1	—	—	—	—	3
Preauricular ear skintag	1[i]	—	1	—	—	1[j]	3
Hipluxation	2	—	—	—	—	—	2
Microcephaly	—	1[a]	1	—	—	—	2
Ptosis	2[h,i]	—	—	—	—	—	2
Others	2[k]	2[l]	1[m]	—	—	1[n]	6

MCA, major congenital malformations.

[a] One case with meningomyelocele, inguinal hernia, and microcephaly.

[b] One case with palpable defect in sacral spinal arches at birth confirmed radiographically, with normal overlying skin.

[c] One case with congenital heart defect and cleft lip + palate.

[d] One case with congenital heart defect, radius aplasia, and hemivertebrae 1, 3, and 5.

[e] One case with cleft lip, hypospadia, and hydrocephalus.

[f] One case with esophageal atresia and preaxial polydactyly.

[g] One case with triphalangeal thumb and hemimelia.

[h] One case with hypospadia and ptosis.

[i] One case with preauricular ear skintag and ptosis.

[j] One case with preauricular fistula.

[k] One case each: hypertrophic pylorus stenosis; asymmetric crying face.

[l] One case each: craniosynostosis; aplasia of first rib and hypersegmentation manubrium sterni.

[m] One case with congenital megacolon.

[n] One case with chylothorax and persistent fetal circulation.

methods used, including diagnosis and ascertainment of patients. For the reanalysis, we obtained the raw data from the individual centers and standardized the criteria for MCA. However, we could not adjust for the nonin-

clusion of stillbirths and neonatal deaths in the Magdeburg study. That study was relatively small (n = 42), and the effect of the exclusion of stillbirths and neonatal deaths on the risk estimates is therefore probably limited.

TABLE 7. *MCA occurring two or more times with use of polytherapy (n ⩾ 20)*

MCA	CBZ ± VPA	PHT + CBZ	PHT + PB	VPA +ESM	PB + CBZ	Others	Any (⩾2)
Total exposures	79	44	40	39	27	287	512
Inguinal hernia	2	—	1	1	—	3	7
Congenital heart defect	—	1[a]	—	—	—	5	6
Cleft lip ± palate	1	—	—	—	—	5	6
Hypospadia	2	1[a]	2[b]	—	—	1	6
Clubfoot	—	—	—	1	1[c]	3[d]	5
Hip luxation	2	1	—	1	—	—	4
Spina bifida occulta/aperta and/or hydrocephalus	1[e]	1[f]	—	—	—	1[d]	3
Microcephaly	—	1[a]	—	—	—	1	2
Others	1[g]	1[h]	2[i]	—	1[c]	7[j]	12

Abbreviations as in Table 3.

[a] One case with congenital heart defect and microcephaly.

[b] One case each: hypospadia and nail aplasia; hypospadia and umbilical hernia.

[c] One case with hydronephrose and clubfeet.

[d] One case with spina bifida aperta and clubfeet.

[e] One case with meningocele and hydrocephalus.

[f] One case with hydrocephalus.

[g] One case with syndactyly of toes digiti II/III.

[h] One case with craniofacial dysostosis.

[i] One case each: unilateral lung aplasia; psychomotor retardation, seizures and strabismus.

[j] One case each: ptosis; IgG deficiency, epilepsy, and heart murmur; thymus aplasia, IgA deficiency, and IgG subclass I deficiency; trigonocephaly; MCA; absent tear ducts; double right ureter.

Furthermore, in the Magdeburg group, no pregnancies had to be excluded because of stillbirth or neonatal death during the study period.

Centers differed with respect to medication prescription and risks of MCA. Differences in risk of MCA may be explained in part by differences among centers in diagnostic procedures used. Because such differences may confound the analysis, we adjusted for study center in the pooled analysis and studied the association between AEDs and MCA (according to the standardized criteria) also within each study center. A higher risk of MCA for children exposed to VPA was detected consistently in all centers that studied VPA, although the risk was not significant in the individual centers, most likely due to the small number of pregnancies exposed. If the association would be due to bias, this must have occurred similarly in all studies, which is plausible only in the case of confounding by indication. Confounding by indication implies that certain types of epilepsy that directly increase the risk of MCA, may require treatment with certain AEDs, leading to a spurious association between the AEDs and the risk of MCA. Indeed, there was evidence of a relation between the type of epilepsy and the prescription of AEDs in the present study. Patients with generalized epilepsy more often were prescribed VPA, ESM, PB, or PRM monotherapy and the combinations of VPA and PB, PRM, and CBZ or VPA and ESM. Patients with partial epilepsy more often received CBZ monotherapy or the combinations of CBZ and PHT, CBZ and VPA, or CBZ and clonazepam. Although it is difficult to exclude confounding by indication in an observational study, we noted no significant evidence of an association between any type of epilepsy and MCA, suggesting that epilepsy type is not likely to explain our results. Finally, bias may be related to the fact that multiple pregnancies in a woman were included. We therefore performed an analysis in which only the first pregnancy of a woman ascertained in the study was included. This did not change any of our conclusions.

VPA has previously been reported to pose an increased risk of MCA. About 10 years after the introduction of VPA, the possibility of teratogenic effects became evident. An association with neural tube defect was observed in mice (35,36). Subsequently, reports of children with neural tube defects after prenatal exposure to VPA were published (33,37–41). A risk of 1–2% was estimated on the basis of retrospective studies (33,38,42) and several small prospective cohort studies (41). The prospective study of Omtzigt et al. (23) suggested a risk as high as 6%. In the pooled analysis, the risk of neural tube defects in offspring of women treated with VPA was 3.8%. Our results, as well as those of animal experiments (43), suggest that VPA dose is important with regard to the degree of risk of neural tube defects. An association between hypospadias and VPA has also been suggested (11,33,44). The current study is inconclusive with regard to this finding (n = 1). The risk of neural tube defects for offspring exposed to CBZ was 1.0%, very similar to the 0.5–1% risk reported earlier (10).

Our reanalysis of data from five prospective studies showed that VPA is consistently associated with an increased risk of MCA in offspring exposed in utero to VPA. An important advantage of the present study is that we were able to reanalyze data of prospective European studies using uniform criteria for the diagnosis of MCA and to determine a dose–response relationship between the occurrence of these MCA and the use of AEDs. For CBZ, we found no evidence of a dose–response relationship, whereas risk remained NS for PB. Our study shows that in particular the offspring of women receiving $\geqslant$1,000 mg/day VPA appear to be at increased risk. Based on the risk estimates, physicians may choose not to use VPA monotherapy during pregnancy if satisfactory seizure control can be achieved with other AEDs; if other AEDs cannot be substituted for VPA, use of daily dosages <1,000 mg/day VPA is recommended whenever results in effective seizure control. Although we pooled the data of five studies, the number of women exposed to a particular AED regimen, especially AED combinations, remains small for a substantial number of AEDs, which results in risk estimates that are not stable. Despite the standardized case definition and gain of statistical power obtained in our reanalysis, the interpretation of our findings is still limited because of the differences in prescribing practices and case ascertainment among centers. Therefore, standardized single-center or multicenter studies with larger numbers of AED-exposed pregnancies remain necessary to allow further quantification of the effect of the other AEDs in the etiology of MCA in the offspring of women with epilepsy.

We recommend performance of multicenter prospective and population-based studies of pregnancy outcome according to a standardized study protocol and standardized study procedures, such as ascertainment procedures, assessment of etiological factors and outcome (including definition of outcome), inclusion and exclusion criteria, and selection of controls (if appropriate). This is especially relevant for the coming decades, in view of the many new AEDs currently entering the market for which no human clinical safety data are available with respect to their use during pregnancy.

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