ORIGINAL ARTICLE

Efficacy of medical care of epileptic pregnant women based on the rate of congenital abnormalities in their offspring

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ABSTRACT   The objective of the present study was to check the efficacy of progress in the medical care of epileptic pregnant women on the basis of the reduction of different congenital abnormalities (CAs) in their offspring. First, the prevalence of medically recorded epilepsy was compared in 95 pregnant women who later had offspring with different CAs (case group) and 90 pregnant women who later delivered newborn infants without CA (control group) and matched to cases in the Hungarian Case-Control Surveillance System of Congenital Abnormalities, 1980–1996. Second, the rate of different CAs was compared in the offspring of epileptic pregnant women between 1980 and 1989 and 1990–1996. Cleft lip with or without cleft palate, cleft palate, cardiovascular CAs, oesophageal atresia/stenosis, hypospadias and multiple CAs showed a higher risk in the offspring of pregnant women with epilepsy treated with different antiepileptic drugs, explained mainly by polytherapy. There was no higher risk for total CAs after monotherapy. There was no significantly lower rate of total CAs in the offspring of epileptic pregnant women during the second period of the study. The efficacy of special medical care of epileptic pregnant women was not shown on the basis of decrease in the rate of CAs in the offspring of epileptic pregnant women.

Key Words: antiepileptic drug treatment, congenital abnormality, epilepsy, pregnancy

INTRODUCTION

Epilepsy is defined as a disorder of the brain function characterized by the periodic and unpredictable occurrence of seizures and is classified as primary generalized, or focal/partial with or without secondary generalization. Primary general seizures can be divided into absence, myoclonic, atonic, or tonic-clonic (Wyllie 2001).

Epilepsy is one of the most frequently studied maternal diseases during pregnancy (Tompson *et al.* 1997; Aminoff 2004). Partly most epilepsies had early onset, and therefore, occured in 0.3–0.6% of pregnant women. Partly the higher rate of structural birth defects (i.e. congenital abnormalities [CAs]) in the children of epileptic women treated with antiepileptic drugs (AEDs) was recognized after the first paper on the topic (Janz and Fuchs 1964) by Meadow (1968) and later confirmed by several studies and completed with minor anomalies, such as broad and low nasal bridge or nail hypoplasia (Shepard and Lemire 2004; Briggs *et al.* 2005) and func-

tional disturbances (e.g. mental retardation) (Meador *et al.* 2009). There was a long debate whether this higher risk associated with epilepsy itself (genetic predisposition or adverse effect of seizures), AEDs, other (e.g. lifestyle) factors, or their interaction. However, Holmes *et al.* (2001) showed that pregnant women with a history of epilepsy, but without AED treatment during pregnancy had no higher risk for CA, though it is worth mentioning that untreated women are expected to be affected with less severe epilepsy (Fried *et al.* 2004).

In the 1980s the preconceptional care of epileptic women was introduced in Hungary (Czeizel 1999; Erős *et al.* 1998) and special prenatal care of epileptic pregnant women was recommended (Tompson *et al.* 1997; Aminoff 2004). The aim of the study was therefore to check the efficacy of this recent progress in the medical care of epileptic pregnant women on the basis of the reduction of CA, thus the data in the two periods of the study (i.e. 1980 and 1989 and 1990–1996) were compared in the population-based dataset of the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) (Czeizel *et al.* 2001).

MATERIALS AND METHODS

Cases affected with CAs were selected from the dataset of the Hungarian Congenital Abnormality Registry (HCAR), 1980–1996 (Czeizel 1997) for the HCCSCA.

Hungarian Congenital Abnormality Registry

Notification of cases with CA is mandatory for physicians from birth until the end of first postnatal year to the HCAR. Most cases are reported by obstetricians and pediatricians. In Hungary, practically all deliveries take place in inpatient obstetric clinics and the birth attendants are obstetricians. Pediatricians work in the neonatal units of inpatient obstetric clinics, or in various inpatient and outpatient pediatric clinics. Autopsy was mandatory for all infant deaths and common (about 80%) in stillborn fetuses during the study period. Pathologists sent a copy of the autopsy report to the HCAR if defects were identified in stillbirths and infant deaths. Since 1984, fetal defects diagnosed in prenatal diagnostic centers with or without termination of pregnancy have also been included into the HCAR.

CAs were differentiated into three groups: lethal (if defects cause stillbirths or infant deaths or pregnancies are terminated due to fetal defect in more than 50% of cases), severe (without medical intervention CAs cause handicap or death) and mild (CAs require medical intervention but life expectancy is good). Lethal and severe CAs together constitute major CAs. (Minor anomalies or morphological variants without serious medical or cosmetic consequences are excluded from the class of CA.) In addition, two main categories of cases with CAs were differentiated: isolated (only one organ is

affected) and multiple (concurrence of two or more CAs in the same person affecting at least two different organ systems).

The total (birth + fetal) prevalence of cases with CA diagnosed from the second trimester of pregnancy through the age of one year was 35 per 1000 informative offspring (live-born infants, stillborn fetuses and electively terminated malformed fetuses) in the HCAR, 1980–1996 (Czeizel 1997) and about 90% of major CAs was recorded in the HCAR during the 17 years of the study period (Czeizel *et al*. 1993). The proportion of live-born infants, stillborn fetuses and electively terminated malformed fetuses was 97.1%, 1.1% and 1.8%, respectively,

Selection of cases and control for the HCCSCA

There were three exclusion criteria of CAs from the HCAR for the dataset of the HCCSCA: (i) cases reported after three months of birth or pregnancy termination (77% of cases were reported during the first three-month time window and the rest included mainly mild CAs); (ii) three mild CAs (congenital dysplasia of hip and inguinal hernia, large hemangioma); and (iii) CA syndromes caused by major mutant genes or chromosomal aberrations with preconceptional origin.

Controls were defined as newborn infants without CA and were selected from the National Birth Registry of the Central Statistical Office for the HCCSCA. In general, two controls were matched to every case according to sex, birth week in the year when cases were born, and district of parents' residence.

Gestational age was calculated from the first day of the last menstrual period.

Collection of exposure data and confounders in the HCCSCA

Prospective medically recorded data

Mothers were asked in an explanatory letter to send us the prenatal maternity logbook and other medical records, particularly discharge summaries concerning their diseases during the study pregnancy and their child's CA. These documents were sent back within one month. Prenatal care was mandatory for pregnant women in Hungary (if a pregnant woman did not visit a prenatal care clinic, she did not receive a maternity grant and leave), thus nearly 100% of pregnant women visited prenatal care clinics, on an average of seven times during their pregnancies. The first visit was between the 6th and 12th gestational weeks. The task of obstetricians was to record all pregnancy complications, maternal diseases (e.g. epilepsy) and related drug prescriptions in the prenatal maternity logbook.

Retrospective self-reported maternal information

A structured questionnaire with a list of medicinal products (drugs and pregnancy supplements) and diseases, plus a printed informed consent form were also mailed to the mothers immediately after the selection of cases and controls. The questionnaire requested information on pregnancy complications and maternal diseases, on medicinal products taken during pregnancy according to gestational months, and on family history of CAs. To standardize the answers, mothers were asked to read the enclosed lists of medicinal products and diseases as a memory aid before they filled in the questionnaire.

The mean ± SD time elapsed between the birth or pregnancy termination and the return of the information package (questionnaire, logbook, discharge summary, and informed consent form) in our prepaid envelope was 3.5 ± 1.2 and 5.2 ± 2.9 months in the case and control groups, respectively.

Supplementary data collection

Regional nurses were asked to visit all non-respondent case mothers at home to help them fill in the same questionnaire and evaluate the

available medical records, as well as obtain data regarding smoking and drinking habits through a cross interview of mothers and their close relatives living together, and finally the so-called 'family consensus' was recorded. Smoking habit was evaluated on the number of cigarettes per day while three groups of drinking habit were differentiated: (i) abstinent or occasional drinkers (less than one drink per week); (ii) regular drinkers (from one drink per week to one daily drink); and (iii) hard drinkers (more than one drink per day). Regional nurses visited only 200 non-respondent and 600 respondent control mothers in two validation studies (Czeizel *et al*. 2003; Czeizel and Vargha 2004) using the same method as in case mothers, because the committee on ethics considered this follow-up to be disturbing to the parents of all healthy children.

Overall, the necessary information was available for 96.3% of cases (84.4% from reply to the mailing, 11.9% from the nurse visit) and 83.0% of the controls (81.3% from reply, 1.7% from visit). Informed consent form was signed by 98% of mothers, and names and addresses were deleted in the remaining 2%.

Herein 17 years of data of the HCCSCA between 1980 and 1996 are evaluated because the data collection has been changed since 1997 (all mothers are visited by regional nurses), and the recent data had not been validated at the time of the analysis.

Diagnostic criteria of epilepsy in pregnant women

Hungarian medical doctors follow the international recommendations at the diagnosis of epilepsy, thus it was based on clinical symptoms, electroencephalograph (EEC) and other examinations. In the first step of our analysis we selected all pregnant women with the diagnosis of epilepsy with or without AEDs. In the second step we differentiated these pregnant women according to the source of information: (i) prospectively and medically recorded epilepsy in the prenatal maternity logbook or in discharge summaries of hospitalized pregnant women; and (ii) epilepsy based on only retrospective maternal information. Practically all epileptic pregnant women were recorded by obstetricians in the prenatal maternity logbook on the basis of the available medical documents. (Only two pregnant women reported on their untreated epilepsy without record in the prenatal maternity logbook; these two women were excluded from the study.) In general, the type of epilepsy was not mentioned in the prenatal maternity logbook.

Epilepsy-related AED treatments were evaluated according the chemical structure of medicinal products.

Among potential confounding factors, maternal age, birth order, marital and employment status as indicators of socio-economic status (Puho *et al*. 2005), other maternal diseases and related drug treatments, as well as folic acid/multivitamin supplementation (Kjaer *et al*. 2008; Czeizel 2009) were considered.

Statistical analysis of data

SAS version 8.02 (SAS Institute, Cary, NC, USA) was used for statistical analyses. Contingency tables were prepared for the main study variables. First, the characteristics of pregnant women with epilepsy were compared with all pregnant women without epilepsy and χ^2 test was used for categorical variables, while Student's *t*-test was used for quantitative variables. Second, AEDs, other maternal diseases and related drug treatments were evaluated by ordinary logistic regression models and odds ratios (OR) with their 95% confidence intervals (CI) were calculated. Third, we compared the prevalence of epilepsy during the study pregnancy in specified CA groups including at least three cases with the prevalence of epilepsy in their all matched control pairs. Adjusted OR with 95% CI were evaluated in conditional logistic regression models for the prevalence of epilepsy. We examined confounding

variables by comparing the OR for epilepsy in the models with and without inclusion of the potential confounding variables. Maternal age (<20 years, 20–29 years, and 30 years or more), birth order (first delivery or one or more previous deliveries), employment status, and folic acid use (yes/no) were included in the models as potential confounders. Finally, the total prevalence of cases with different isolated CAs and with multiple CAs was compared in epileptic mothers according to the birth year of cases between 1980 and 1989 and 1990–1996.

RESULTS

The total dataset is presented. Of 22 843 cases, 95 (0.42%), while of 38 151 controls without CA, 90 (0.24 %) had mothers with medically recorded epilepsy in the prenatal maternity logbook (OR with 95% CI: 1.8, 1.3–2.4).

Table 1 summarizes the characteristics of epileptic mothers of cases and controls, in addition to non-epileptic mothers as reference. Epileptic mothers were somewhat younger compared to non-epileptic mothers. The mean birth order was similar in control mothers with or without epilepsy, but was lower in epileptic case mothers than in non-epileptic case mothers. The proportion of unmarried epileptic women was larger with a lower proportion of professional/managerial/skilled worker employment status.

The use of folic acid was lower in epileptic mothers than in non-epileptic mothers. In addition, the occurrence of folic acid supplementation was less frequent in epileptic case mothers than in epileptic control mothers (OR with 95% CI: 0.7, 0.5–0.9). Supplementation with folic acid-containing multivitamins occurred rarely in the study groups.

Table 2 summarizes the estimated associations between maternal epilepsy and different CAs in their offspring; in addition these epileptic pregnant women were differentiated according to without treatment, with mono- and polytherapy. A higher risk of cleft lip with or without cleft palate, cleft palate, cardiovascular CAs, oesophageal atresia/stenosis (though based on only three cases) and hypospadias was observed in the children of epileptic pregnant women. Thus, the total rate of CAs was also higher.

Only 12 epileptic case mothers were recorded without AED treatment during the study pregnancy, their offspring were affected

Table 1 Maternal characteristics of case and control mothers with epilepsy and without epilepsy as reference

| | Case mothers | | | | Control mothers | | | |
| | Without epilepsy (N = 22 748) | | With epilepsy (N = 95) | | Without epilepsy (N = 38 051) | | With epilepsy (N = 90) | |
Variables Quantitative	No.	%	No.	%	No.	%	No.	%
Maternal age (years)								
19 or less	2 494	11.0	12	12.6	3 271	8.6	6	6.7
20–29	15 525	68.2	68	71.6	27 531	72.3	71	78.9
30 or more	4 729	20.8	15	15.8	7 259	19.1	13	14.4
Mean ± SD	25.5 + 5.3		24.6 + 4.6		25.5 + 4.9		24.9 + 4.5	
Birth order								
1	10 654	46.8	54	56.8	18 156	47.7	53	58.9
2 or more	12 094	53.2	41	43.2	19 905	52.3	37	41.1
Mean ± SD	1.9 + 1.1		1.6 + 0.8		1.7 + 0.9		1.7 + 1.2	
Categorical	No.	%	No.	%	No.	%	No.	%
Unmarried	1 258	5.5	11	11.6	1 462	3.8	10	11.1
Employment status								
Professional	1 972	8.7	5	5.3	4 418	11.6	5	5.6
Managerial	5 078	22.3	19	20.0	10 245	26.9	20	22.2
Skilled worker	6 479	28.5	22	23.2	11 885	31.2	23	25.6
Semiskilled worker	4 178	18.4	19	20.0	6 145	16.1	16	17.8
Unskilled worker	1 766	7.8	10	10.5	2 177	5.7	10	11.1
Housewife	2 398	10.5	8	8.4	2 343	6.2	11	12.2
Other	877	3.9	12	12.6	848	2.2	5	5.6
Pregnancy supplements								
Iron	14 688	64.6	54	56.8	26 716	70.2	55	61.1
Calcium	1 799	7.9	4	4.2	3 578	9.4	5	5.6
Folic acid	11 245	49.4	34	35.8	20 731	54.5	44	48.9
Vitamin B6	2 004	8.8	9	9.5	4 076	10.7	10	11.1
Vitamin D	6 084	26.7	17	17.9	10 133	26.6	17	18.9
Multivitamins	1 325	5.8	5	5.3	2 500	6.6	9	10.0

Table 2 Estimation of the association between maternal epilepsy during pregnancy and different congenital abnormalities (CAs) on the basis of comparisons of cases and all matched controls, as well as according to the type of treatment

Study group	Grand total no.	Epilepsy				Without treatment		Monotherapy				Polytherapy			
		No.	%	OR	95% CI†	No.	%	No.	%	OR	95% CI†	No.	%	OR	95% CI†
Controls	38 151	90	0.24	Reference		10	0.03	50	0.13	Reference		30	0.08	Reference	
Isolated CAs															
Neural-tube defects	1 202	7	0.58	1.9	0.8–4.4	1	0.08	4	0.33	1.5	0.3–6.8	2	0.17	2.0	0.2–14.0
Cleft lip‡	1 375	11	0.80	**3.4**	**1.8–6.4**	0	0.00	2	0.15	1.2	0.3–4.8	9	0.65	**8.7**	**4.1–18.3**
Cleft palate	601	5	0.83	**3.5**	**1.4–8.8**	0	0.00	2	0.33	2.7	0.6–11.0	3	0.50	**6.6**	**2.1–21.7**
Cardiovascular CAs	4 480	25	0.56	**2.4**	**1.5–3.7**	5	0.11	8	0.18	1.4	0.7–3.0	12	0.27	**3.5**	**1.8–6.9**
Oesophageal atresia/stenosis	217	3	1.38	**5.9**	**1.9–18.9**	0	0.00	2	0.92	**7.4**	**1.8–30.7**	1	0.46	6.1	0.8–45.2
Hypospadias	3 038	13	0.42	**1.8**	**1.0–3.3**	3	0.10	7	0.23	1.8	0.8–4.1	3	0.10	1.3	0.4–4.3
Undescended testis	2 052	7	0.34	1.4	0.7–3.1	0	0.00	6	0.29	1.3	0.9–5.4	1	0.05	0.6	0.1–4.7
Clubfoot	2 424	5	0.21	0.9	0.4–2.2	0	0.00	4	0.17	1.3	0.5–3.6	1	0.04	0.5	0.1–4.0
Poly/syndactyly	1 744	5	0.29	1.2	0.5–3.0	2	0.11	1	0.06	0.5	0.1–3.3	2	0.11	1.5	0.4–6.3
Other isolated CAs	4 361	9§	0.21	0.9	0.5–1.7	1	0.02	4	0.09	0.8	0.3–2.1	4	0.09	1.0	0.3–13.3
Multiple CAs	1 349	5	0.37	1.6	0.6–3.9	0	0.00	1	0.07	0.6	0.1–4.3	4	0.30	**3.9**	**1.4–11.1**
Total	22 843	95	0.42	**1.8**	**1.3–2.4**	12	0.05	41	0.18	1.4	0.9–2.2	42	0.18	**2.4**	**1.5–3.9**

†OR adjusted for maternal age and employment status, birth order, folic acid use during pregnancy in conditional logistic regression model; ‡Cleft lip with or without cleft palate; §Congenital pyloric stenosis 2, microtia 1, lung hypoplasia 1, intestinal atresia 1, vaginal atresia 1, exomphalos 1, torticollis 1, pectus excavatum 1.
Bold numbers show significant associations.

Table 3 Controls and cases born to mothers with monotherapy, polytherapy and without treatment according to antiepileptic drug

Antiepileptic	Control	NTD	CLP	CP	CCM	OAT	SH	UT	CF	PY/SY	Others	MCA	Total
					Monotherapy								
Carbamazepine (Ca)	10	2	0	0	4	0	1	0	2	0	0	0	8
Clomethiazol (Cl)	0	0	0	0	1	1	0	0	0	0	0	0	2
Clonazepam (Cz)	1	0	0	0	0	0	0	0	0	0	0	0	0
Diazepam (Di)	4	0	0	1	0	0	1	0	0	0	0	0	2
Ethosuximide (Et)	0	0	1	0	0	1	0	0	0	0	0	0	2
Mephenytoin (Me)	2	0	0	0	0	0	0	0	0	0	0	0	0
Morsumide (Mo)	2	0	0	0	0	0	0	0	0	0	0	0	0
Phenacemide (Pa)	0	0	0	0	0	0	0	0	0	0	0	0	0
Phenobarbital (Pb)	0	0	0	0	0	0	0	1	0	0	0	0	1
Phenytoin (Pt)	19	1	1	1	3	0	2	3	1	0	2†	0	14
Primidone (Pr)	6	0	0	0	0	0	0	1	1	0	1‡	1	4
Sultiame (Su)	0	0	0	0	0	0	0	0	0	0	0	0	0
Trimethadione (Tr)	1	0	0	0	0	0	0	0	0	1	0	0	1
Valproate (Va)	5	1	0	0	0	0	3	1	0	0	1§	0	7
Total	50	4	2	2	8	2	7	6	4	1	4	1	41
Polytherapy	30	2	9	3	12	1	3	1	1	2	4	4	42
No drug treatment	10	1	0	0	5	0	3	0	0	2	1	0	12
Grand total	90	7	11	5	25	3	13	7	5	5	9	5	95

†Exomphalos, atresia of bile duct; ‡Branchial cyst; §Microtia.

CCM, cardiovascular congenital abnormalities (CAs); CF, clubfoot; CLP, cleft lip with or without cleft palate; CP, cleft palate; MCA, multiple CA; NTD, neural-tube defect; OAT, oesophageal atresia/stenosis; PY/SY, poly/syndactyly; SH, hypospadias; UT, undescended testis.

with three different CAs: five cases with cardiovascular CA (crude OR with 95% CI: 3.3, 1.2–9.2), three cases with hypospadias, two cases with poly/syndactyly and one case with anencephaly, thus OR (with 95% CI) was 1.3 (0.7–3.4) for total CA group.

Of 95 epileptic pregnant women, 41 were treated with one AED (Table 2), and this monotherapy associated with a higher risk with oesophageal atresia/stenosis, but this association was based on two cases. However, it is important to mention that there was no significantly higher risk for the total group of CAs and any other CA group. The offspring of 42 epileptic pregnant women with polytherapy had a high risk for cleft lip with or without cleft palate, cleft palate, cardiovascular CA and multiple CAs, thus the risk was also higher for total CA group (Table 2).

Table 3 shows the numerical distribution of different CAs according to AEDs used in monotherapy. Of eight cases with cardiovascular CA, four had mothers with carbamazepine, while three were treated with phenytoin. Of seven cases with hypospadias, three had epileptic mothers treated with valproate and two were treated with phenytoin. Of six cases with undescended testis, three had epileptic mothers with phenytoin treatment. Of four cases with neural-tube defect, two had mothers with carbamazepine, one with phenytoin and one with valproate treatment. However, the most impressive finding is the low number of cleft palate and cleft lip with or without cleft palate after monotherapy.

The different combinations of AEDs in polytherapy are shown in Table 4. Most frequently, primidone, phenytoin and carbamazepine were used, followed by diazepam and sultiame. Phenytoin and diazepam occurred most frequently in polytherapy in the group of

Table 4 Antiepileptic drugs used in polytherapy according to different congenital abnormalities (CAs)

CA group	Specified CA = antiepileptic drugs
NTD	Spina bifida = 2: *Va* + Pr, *Va* + Ca + Pr
CLP	Cleft lip = 6: *Pt* + Di, *Pt* + Pr, *Pt* + Ca + Su, Di + Pr, Di + Ca + Me, Pr + Tr + Su
	Cleft lip with cleft palate = 3: *Pt* + Di, *Pt* + Pr, *Pt* + Ca + Di + Su + Me
CP	Cleft palate = 3: *Ca* + Di, *Ca* + Tr, *Ca* + Pr + Pb
CCM	Ventricular septal defect = 8: Pt + Di, Pt + *Pr* + Me, Di + Su + *Pr*,
	Di + Su + Mo, Ca + Su + Pb, *Pr* + Su, *Pr* + Et, *Pr* + Me + Pa
	Atrial septal defect = 1: Pt + *Pr* − Di
	Unspecified = 3: Pt + Me, Pt + Di + Ca, Di + Ca + *Pr* + Et
OAT	Oesophageal atresia with oesophageal – tracheal fistula = 1: Ca + Va + Su
SH	Hypospadias = 3: Pt + Di, *Va* + Di, *Va* + Di

The abbreviations of different CAs and antiepileptic drugs are shown in Table 3.

The abbreviations of most frequently used drugs are printed in italic.

cleft lip with or without cleft palate. Interestingly, cleft palate showed a different pattern because carbamazepine was the common component in the polytherapy of this CA group. The most frequent components of polytherapy were primidone and phenytoin in the group of cardiovascular CAs with an obvious dominance of ventricular septal defect. In the group of neural-tube defects valproate and primidone were components of polytherapy in both cases. In the group of hypospadias, diazepam and valproate were the leading components of polytherapy. Some drugs, such as clonazepam, mephenytoin, morsumide, phenacemide and sultiame were used only in polytherapy.

The combined effect of different AEDs in mono- and polytherapy confirmed the well-known teratogenic effect of valproate, phenytoin and primidone. In addition, our data indicated the teratogenic effect of sultiame (OR with 95% CI: 5.7, 1.6–14.4). However, the risk of CAs did not reach the level of significance after the use of carbamazepine (OR with 95% CI: 1.9, 0.9–4.3). The number of pregnant women with trimethadione treatment was too small for evaluation. These Hungarian data did not confirm the teratogenic potential of phenobarbital (OR with 95% CI: 1.3, 0.6–2.6) and diazepam (OR with 95% CI: 1.1, 0.7–1.7).

In the second step of the study we compared the data of cases with CAs between 1980 and 1989 and 1990–1996. There was no significant change in maternal characteristics of epileptic pregnant women between the two study periods.

Table 5 summarized the data of different CAs in the offspring of pregnant women without treatment, as well as with mono- and polytherapy between 1980 and 1989 and 1990–1996. The number of mono- and polytherapy was 28:31 between 1980 and 1989, while this ratio was 13:11 between 1990 and 1996 thus the proportion of polytherapy decreased but it was far from the level of significance ($P = 0.58$). In addition, there was a decrease in the total rate of CAs from 0.44 % to 0.36% (OR with 95% CI: 0.82, 0.56–1.13), that is, this decline was about 20% due to the decrease in their rate both after mono- and polytherapy in the second period of the study. It is worth mentioning the lack of cases with cleft palate in the second period.

The comparison of different antiepileptic drug uses between the two study periods (Table 6) shows that the use of carbamazepine and mainly valproate increased, while the use of phenytoin decreased in epileptic mothers. On the other hand these data indicate that the reduction of polytherapy occurred mainly in control mothers.

DISCUSSION

The aim of the study was to check the efficacy of recent progress in the care of epileptic pregnant women. Our data showed some increase in the proportion of recommended monotherapy and a 20% reduction in the risk for total CAs during the second period of the study. Thus, a real breakthrough in the efficacy of recent medical care of epileptic pregnant women regarding the teratogenic risk of AED has not been found.

In the total material, a higher risk for total CAs was found only after polytherapy, explained mainly by the higher rate of cleft lip with or without cleft palate, cleft palate, cardiovascular CAs and multiple CAs. Thus, the lower teratogenic potential of monotherapy was confirmed. In addition this study confirmed the teratogenic effect of phenytoin, valproate, primidone and completed this list with the teratogenic effect of sultiame (Czeizel *et al.* 1992). However, this Hungarian material did not confirm the

teratogenic effect of carbamazepine, diazepam and phenobarbital. The recognition of mild teratogenic potential of carbamazepine depends on the number of pregnant women (i.e. statistical power).

The teratogenic potential of diazepam and phenobarbital depends on the indication of these drugs (i.e. underlying maternal diseases). The recent Cochrane review of these drugs has not confirmed their teratogenic potential (Adab *et al.* 2004). A population-based monitoring system of self-poisoning pregnant women (i.e. pregnant women who attempted suicide with extremely large doses of drugs) was established in Budapest (Czeizel *et al.* 2008). Among 1044 self-poisoned pregnant women, 112 used very large doses of diazepam (25–800 mg) and 37 women attempted suicide between the 4th and 12th gestational weeks, but a higher rate of CAs was not detected (Gidai *et al.* 2008). In addition, 88 pregnant women attempted suicide with very large doses of phenobarbital and 34 women between the 4th and 12th gestational weeks, but a higher risk of CAs was not found (Timmemann *et al.* 2009).

The strengths of the HCCSCA are that is a population-based large dataset including 185 pregnant women with prospectively and medically recorded epilepsy in an ethnically homogeneous European (Caucasian) population. We were able to differentiate the different groups of AEDs in the study pregnancies. Additional strengths are the matching of cases to controls without CA; available data for potential confounders, and finally that the diagnosis of medically reported CAs was checked in the HCAR (Czeizel 1997) and later modified, if necessary, on the basis of recent medical examination within the HCCSCA (Czeizel *et al.* 2001).

However, this dataset also has limitations: (i) We did not know any details regarding the onset of epilepsy before the study pregnancy; (ii) Other pregnancy outcomes (e.g. miscarriages) were not known; (iii) Unfortunately, our dataset is not appropriate for the evaluation of functional defects (e.g. valproate associates with the most severe mental retardation-inducing effect); (iv) In general, the doses of AEDs drugs used for the treatment of epileptic pregnant women were not known, but the results of our validation studies showed that recommended doses were used in most pregnant women (Czeizel *et al.* 2003); (v) The data of blood level of AEDs were not recorded in the HCCSCA; and (vi) The major weakness of our study is that the recent data of pregnant women (i.e. after 1996) are not available in the HCCSCA.

The major message of this study and some other recent papers is that pregnancy in epileptic women does not need to be discouraged if these women wish to have babies, but epileptic women need a specific and high standard of medical care.

The first task is to educate epileptic women to understand that it is necessary to prepare their pregnancies before conception. There are many tasks during this preconceptional period: (i) Check their AEDs and attempt changing the teratogenic drugs (e.g. valproate) to less (e.g. carbamazepine) or non-teratogenic (lamotrigine) drugs under control of specialists. However, at the selection of AEDs for epileptic pregnant women the type of epilepsy is the most important aspect, but some other aspects (e.g. the duration previous seizure-free interval, other diseases) can also be considered; (ii) In general, monotherapy is better because polytherapy associates with a higher risk of CAs (Källen 1986, Meador *et al.* 2008) as in our study; (iii) The use of the lowest effective dose of the given drug is preferable, because higher doses of AEDs associate with a higher risk of specific CAs; (iv) However, it is important to stress that the cluster of seizures during pregnancy in untreated or inappropriately treated epileptic

Table 5 Comparison of epileptic pregnant women without treatment (no treat), with monotherapy (mono) and polytherapy (poly) in the control group and in the case group including cases with different congenital abnormalities (CAs) during the two study periods: 1980–1989 and 1990–1996

Study group	1980–1989										1990–1996									
		No treat		Mono		Poly		Total			No treat		Mono		Poly		Total	
	N	No.	%	No.	%	No.	%	No.	%	N	No.	%	No.	%	No.	%	No.	%
Controls	25 349	7	0.03	23	0.09	22	0.09	52	0.21	12 803	3	0.02	27	0.21	8	0.06	38	0.30
Isolated CAs																		
Neural-tube defects	1 023	0	0.00	4	0.39	1	0.01	5	0.49	179	1	0.56	0	0.0	1	0.56	2	1.12
Cleft lip†	873	0	0.00	1	0.11	7	0.80	8	0.92	502	0	0.00	1	0.20	2	0.40	3	0.60
Cleft palate	412	0	0.00	2	0.49	3	0.73	5	1.21	189	0	0.00	0	0.00	0	0.00	0	0.00
Cardiovascular CAs	2 664	2	0.08	5	0.19	10	0.38	17	0.64	1816	3	0.17	3	0.17	2	0.11	8	0.44
Oesophageal atresia/stenosis	146	0	0.00	2	1.37	0	0.00	2	1.37	71	0	0.00	0	0.00	1	1.41	1	1.41
Hypospadias	1 846	1	0.05	2	0.11	2	0.11	5	0.27	1192	2	0.17	5	0.42	1	0.08	8	0.67
Undescended testis	1 267	0	0.00	5	0.19	0	0.00	5	0.39	785	0	0.00	1	0.13	1	0.13	2	0.25
Clubfoot	1 614	0	0.00	3	0.19	1	0.06	4	0.25	811	0	0.00	1	0.06	0	0.00	1	0.14
Poly/syndactyly	1 042	2	0.19	0	0.00	1	0.10	3	0.29	702	0	0.00	1	0.14	1	0.14	2	0.28
Other isolated CAs	2 770	1	0.04	3	0.11	3	0.11	7	0.25	1590	0	0.00	1	0.06	1	0.06	2	0.13
Multiple CAs	951	0	0.00	1	0.11	3	0.32	4	0.42	398	0	0.00	0	0.00	1	0.25	1	0.25
Total	14 608	6	0.04	28	0.19	31	0.21	65	0.44	8235	6	0.07	13	0.16	11	0.13	30	0.36

†Cleft lip with or without cleft palate.

Table 6 Comparison of uses of different antiepileptic drugs in the two study periods: 1980–1989 and 1990–1996

| | 1980–1989 | | | | 1990–1996 | | | | Total | | | |
| | Controls | | Cases | | Controls | | Cases | | Controls | | Cases | |
Monotherapy	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Carbamazepine	4	7.7	3	4.6	6	15.8	5	16.7	10	11.1	8	8.4
Clomethiazol	0	0.0	2	3.1	0	0.0	0	0.0	0	0.0	2	2.1
Clonazepam	1	1.9	0	0.0	0	0.0	0	0.0	1	1.1	0	0.0
Diazepam	1	1.9	1	1.5	3	7.9	1	3.3	4	4.4	2	2.1
Ethosuximide	0	0.0	2	3.1	0	0.0	0	0.0	0	0.0	2	2.1
Mephenytoin	2	6.7	0	0.0	0	0.0	0	0.0	2	2.2	0	0.0
Morsuximide	1	1.9	0	0.0	1	2.6	0	0.0	2	2.2	0	0.0
Phenacemide	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Phenobarbital	0	0.0	1	1.5	0	0.0	0	0.0	0	0.0	1	1.1
Phenytoin	11	21.2	13	20.0	8	21.1	1	3.3	19	21.1	14	14.7
Primidone	2	3.8	4	6.2	4	10.5	0	0.0	6	6.7	4	4.2
Sultiame	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Trimethadione	0	0.0	1	1.5	1	2.6	0	0.0	1	1.1	1	1.1
Valproate	1	1.9	1	1.5	4	10.5	6	20.0	5	5.6	7	7.4
Total	23	44.2	28	43.1	27	71.1	13	43.3	50	55.6	41	43.2
Polytherapy	22	42.3	31	50.0	8	21.1	11	36.7	30	33.3	42	44.2
No. treatment	7	13.5	6	9.2	3	7.9	6	20.0	10	11.1	12	12.6
Grand total	52	100.0	65	100.0	38	100.1	30	100.0	90	100.0	95	100.0

women associates with an even higher risk of fetal defects (Meador *et al.* 2008). Thus, epileptic pregnant women need treatment during pregnancy as well.

The second task is the monitoring of health status of epileptic pregnant women and their fetuses. The relation of epilepsy and pregnancy is variable, about 45% of pregnant women have a higher seizure frequency, while about 5% associate with a reduced seizure frequency, thus epilepsy remains unchanged in about 50% of pregnant women (Knight and Rhind 1975). The higher risk for seizure is explained by generally declined serum levels of AEDs in pregnancy, therefore an increase in dosage is frequently required during pregnancy to maintain the effective plasma level of AEDs (Tompson *et al.* 1997). Another task is the monitoring of the fetal development with high-resolution ultrasound because the principal defects associated with different teratogenic AEDs, such as neural-tube defects (Meador *et al.* 2008) and fetal hydantoin/dilantin/phenytoin, fetal trimethadione and fetal valproate syndrome/effect (Jones 1988) are detectable approximately at the 20th gestational week. These defects are rarely diagnosed, but pregnant women have the right to decide to keep or terminate their pregnancies after their diagnosis.

The final task is connected with the preparation of delivery, including maternal ingestion of vitamin K1 (10 mg per day) because clinical or subclinical coagulopathy may occur in newborn infants (Aminoff 2004).

In conclusion, the main experience of this study is that the above principles have not been followed in many Hungarian pregnant women, therefore, the efficacy of recent special medical care of epileptic mothers was not obvious in the reduction of CAs.

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