

Pregnancy and teratogenicity of antiepileptic drugs

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Abstract

Maternal use of antiepileptic drugs (AEDs) during pregnancy has been associated with an increased risk of congenital abnormalities in the fetus. This is partly attributable to AEDs.

We aimed to analyse seizure frequency and the rate and type of any congenital malformation related to pregnancies in women with epilepsy in this prospective study. Eighty four pregnant women with epilepsy on AEDs were followed for congenital malformations. Z test was used for statistical analysis. Pregnancy did not influence the seizure frequency in 64 (76.2%) pregnancies. The seizure frequency increased in 16 (19.04%) pregnancies. In 4 (4.76%) pregnancies the number of seizures decreased during pregnancy. Overall percentage of congenital malformations in infants of mothers with epilepsy treated with AEDs was 10%, versus 3.65% in the general Turkish population. Percentages of malformations in children of pregnancies in women with epilepsy on antiepileptic drugs (AEDs) were ; 6.52% (3/46) for carbamazepine (CBZ), 14.28% (2/14) for phenytoin (PHT), 13.33% (2/15) for valproic acid (VPA) and 20% (1/5) for phenobarbital (PB).

This confirms previous reports that all four AEDs (CBZ, PHT, VPA, PB) are associated with an increased risk of congenital malformations, although CBZ seems to be the safest agent in monotherapy.

Key words : Pregnancies in women with epilepsy ; teratogenicity ; antiepileptic drugs ; women with epilepsy ; infants of mother with epilepsy.

Introduction

Epilepsy is a common neurological condition affecting 0.6-1% of the general population (Samren and Lindhout, 1997). Approximately 20% of this group are women of child-bearing age (Legros *et al.*, 2003). The treatment of women of childbearing age who have epilepsy raises questions because of the interactions between epilepsy, antiepileptic therapy and different aspects of reproductive life (Palmieri and Canger, 2002). Prevalence of epilepsy in the pregnant women was reported as 0.3 to 0.6% (Yerby, 1991 ; Nulman *et al.*, 1999 ; Legros *et al.*, 2003). One in every 250 newborns has a mother with epilepsy who requires treatment with an

antiepileptic drug (AED) (Lindhout and Omtzigt, 1992). Due to side effects of AEDs, seizure frequency change and fetal malformation possibility, pregnancies in women with epilepsy are recognized as pregnancies associated with medical risks. The incidence of congenital malformations among infants of mothers with epilepsy treated with AEDs during pregnancy (especially in the first trimester of the pregnancy when the organogenesis occur) is higher than those among infants of normal controls and among infants of mothers with epilepsy whose mothers were not treated (Dansky *et al.*, 1982 ; Nakane, 1982 ; Lindhout *et al.*, 1982). However, animal teratology may not be a reliable predictor of human teratogenicity, and there is a significant lack of information regarding the teratogenic profile of these newer agents in humans (Palmieri and Canger, 2002). Although seizure frequency returns to the characteristics of pregestational period, it was reported earlier that the frequency increases during pregnancy (Caputo and Salvi, 2001).

Many factors that may contribute to the developing of malformations include genetic predispositions, harmful effects of drug metabolites, drug interference with folate metabolism, depression of cardiorespiratory function, and fetal hypoxia due to maternal seizures. The aim of the present study was to evaluate the effects of pregnancy on seizure frequency, the rate of malformations in infants of mothers with epilepsy, the possible teratogenic effect of AEDs, and the possible relationship between types of AEDs and types of malformations.

Methods and materials

This study was designed prospectively from March 1996 to April 2006 in Gulhane Hospital. Eighty four pregnant women with epilepsy on AEDs were included. Only pregnant women with epilepsy who delivered at this hospital and had complete medical records were included in the study. Diagnosis of epilepsy was made before pregnancy in each patient. All the epileptic women hoping to become pregnant were told about the possible effects of epilepsy and AEDs on the baby

and the course of pregnancy. All of the patients received folic acid supplements of 5 mg/day per oral during pregnancy.

Maternal seizure types and epilepsy syndromes were determined from seizure history and clinical studies. Seizure frequency in the last year before pregnancy was compared to the frequency during pregnancy. All the subjects included, kept seizure diaries.

An obstetrician and a neurologist examined pregnant women with epilepsy monthly. After delivery, all of the babies were examined in detail by a pediatrician and the babies who were suspected to have a congenital malformation were referred to advanced clinical examination. AEDs and daily dosage during pregnancy were as follows ; carbamazepine in 49 patients (mean 489.79 mg/day, range 200-1200 mg), phenytoin in 14 patients (mean 250 mg/day, range 200-400 mg), valproic acid in 16 patients (mean 740.62 mg/day, range 500-1500 mg) and phenobarbital in 5 patients (mean 200 mg/day, range 100-300 mg).

For all of the patients, age of first seizure, age of pregnancy, cause of epilepsy, seizure frequency, type of seizure, kind of antiepileptic drug and dosage, serum levels of AEDs, type of birth and congenital malformation were recorded.

STATISTICAL ANALYSIS

Only numbers of cases were reported as descriptive statistics. For the comparison we used "z test". P values less than or equal to 0.05 were evaluated as statistically significant (Zar, 1996).

Results

Eighty four pregnant women with epilepsy on AEDs were studied prospectively. Mean duration of epilepsy of the pregnant women was 12.6 (range 8-15 years) and mean maternal age at delivery was 26.1 (range 18-33 years), mean follow-up period of the subjects was 4.2 (range 3-10 years). Four of the

84 pregnant women with epilepsy underwent the medical abortion in the first trimester on their own will because of the anticipation anxiety toward the horror of the malformative baby. In all of the patients, serum levels of the AEDs were within normal ranges. Pregnancy did not influence the seizure frequency in 64 (76.2%) pregnancies. The seizure frequency increased in 16 (19.04%) pregnancies. In 4 (4.76%) pregnancies the number of seizure decreased during pregnancy (Table 1). In 35 of 84 (41.66%) pregnant women with epilepsy seizures were observed only in the first trimester. During the deliveries, no seizures and fetal trauma were observed in any of the patients.

In our study, 81 (96.43%) women had idiopathic epilepsy and 3 (3.57%) had symptomatic epilepsy. All of the pregnant women with epilepsy were on monotherapy. Observed seizures types of 84 patients during pregnancy were as follows : primary generalized seizures (PGS) in 48 (57.14%), complex partial seizure (CPS) in 8 (9.52%), simple partial seizure (SPS) in 2 (2.38%) and mixed types of seizures (PGS + CPS or myoclonic seizure) in 26 (30.96%) (Table 1).

Of the 80 pregnant women with epilepsy, whose deliveries were in term, 43 (53.75%) had normal deliveries and 37 (46.25%) had sectio cesarean. In all of these deliveries, 72 (90%) babies were healthy and 8 (10%) had congenital malformations. Eight of eighty (10%) infants of mothers with epilepsy treated with AEDs had congenital malformations, consisting of patent foramen ovale, cleft lip with cleft palate, cleft lip, cleft palate, dermal hemangioma, ureterocele and two hypospadias. Four of the 8 epileptic mothers with congenital malformed babies had PGS, 3 had mixed types of seizures, and one had CPS. Mothers with epilepsy who delivered children with ureterocele and dermal hemangioma malformations had no seizures during pregnancy. Three mothers who delivered children with cleft palate, patent foramen ovale and cleft lip experienced seizures in all tree trimesters. Three mothers who delivered children with cleft lip with

Table 1

The characteristics of pregnant women with epilepsy

AED	Mean dose of AED (mg/d)	Number of pregnant	Seizure type				Seizure during the pregnancy			Delivery type		Pregnancy outcome		
			PGS	CPS	SPS	Mixed	Inc	Dec	Same	NB	CS	H	C	CM
PHT	250	14	14	–	–	–	2	2	10	9	5	12	–	2
CBZ	489.79	49	24	8	2	15	8	1	40	26	20	43	3	3
VPA	740.62	16	7	–	–	9	6	–	10	6	9	13	1	2
PB	200	5	3	–	–	2	–	1	4	2	3	4	–	1
Total	–	84	48	8	2	26	16	4	64	43	37	72	4	8

AED : Antiepileptic Drug, PHT : Phenytoin, CBZ : Carbamazepine, VPA : Valproic acid, PB : Phenobarbital, PGS : Primary Generalized Seizure, CPS : Complex Partial Seizure, SPS : Simple Partial Seizure, Mixed : PGS + CPS or myoclonic seizure, NB : Normal Birth, CS : Sectio Cesarean, H : Healthy, C : Curettage, CM : Congenital Malformation, Inc : Increased, Dec : Decreased.

Table 2

The characteristics of the mothers with epilepsy who delivered children with malformation

Case	AED (mg/day)	Seizure type	Number of seizure			Anomalies
			Trimester 1	Trimester 2	Trimester 3	
1	PHT (400)	PGS	1	1	2	Cleft palate
2	PHT (300)	PGS	1	3	3	Patent foramen ovale
3	CBZ (400)	CPS	-	-	-	Ureterocele
4	CBZ (1200)	Mixed	-	-	-	Dermal hemangioma
5	CBZ (400)	PGS	-	1	1	Hypospadias
6	VPA (1000)	Mixed	2	1	1	Cleft lip
7	PB (200)	PGS	-	1	1	Cleft lip with cleft palate
8	VPA (1200)	Mixed	-	1	1	Hypospadias

AED : Antiepileptic Drug, PHT : Phenytoin, CBZ : Carbamazepine, VPA : Valproic acid, PB : Phenobarbital, PGS : Primary Generalized Seizure, CPS : Complex Partial Seizure, Mixed : PGS + CPS or myoclonic seizure.

cleft palate and hypospadias experienced seizures in last two trimesters (Table 2).

In 80 epileptic pregnant using AEDs who delivered at term, percentage of children with malformation were as follows : 14.28% (2 of 14) for PHT, 6.52% (3 of 46) for CBZ, 13.33% (2 of 15) for VPA and 20% (1 of 5) for PB. Cause of the epilepsy in the mothers of malformed baby group was defined as idiopathic.

Discussion

Monotherapy is the cardinal rule for control of seizures in the pregnancies in women with epilepsy. In a meta-analysis study of Matalon *et al.* (2002), 1255 patients were examined for the teratogenicity of CBZ. They found teratogenicity as 5.52% (44/797) for CBZ group and 2.34% (88/3756) in the control group. In the same study, in pregnant women with epilepsy without using AEDs, teratogenicity was found 2.75% (5/182). In patients using CBZ plus one other AED, babies with malformations were seen in 8.57% (18/210). The percentage for polytherapy (CBZ+2 to 4 other AEDs) was 18.18%. Some studies have suggested there is an association between carbamazepine and congenital malformations in about the same frequency for barbiturates and phenytoin but the patterns of malformation are different (Bertollini *et al.*, 1987). Many epidemiologic studies have been carried out and are still being performed and, so far, most of them have shown a two to threefold increase in the risk of congenital malformations in the offspring of epileptic mothers using AEDs during pregnancy compared with the general population. All major anticonvulsant drugs are teratogenic but the risk increases when the mother is on polytherapy especially if sodium valproate is in the combination (Bertollini *et al.*, 1987).

A significant proportion of women with epilepsy have an increase in seizure frequency during pregnancy (Schmidt *et al.*, 1983 ; Yerby, 1991 ; Yerby *et al.*, 1992 ; Yerby, 1992). There are several hypotheses explaining this increase such as hormonal (increase in serum oestrogens), metabolic (increased sodium and water retention), psychological (increased stress and anxiety), physiological (sleep deprivation), and pharmacokinetic mechanisms. However decrease in plasma drug concentration, is probably the most frequent cause (Devinsky and Yerby, 1994 ; Samren and Lindhout, 1997). In studies reporting an increase of epileptic seizures of 17 to 37%, also informed that this precipitation possibly resulted from sleep deprivation and loss of AED compliance with hostile reactions about its side effects related with the pregnancy (Egenaes, 1982 ; Schmidt *et al.*, 1982 ; Nelson and Ellenberg, 1982 ; Tanganelli and Regesta, 1992). Our study showed that the seizure frequency increased in 19.04%, decreased in 4.76% and remained the same in 76.2% of the patients (Table 1).

Over 90% of women with epilepsy will deliver healthy children ; free of congenital malformations (Yerby, 1991 ; Delgado-Escueta and Janz, 1992 ; Eller *et al.*, 1997). The rate of congenital malformations in infants of epileptic mothers is 2-3 times higher than in an average population. Malformation rates in the general population range from 2 to 3% (Yerby, 1991 ; Yerby, 2003). Malformation percentage in the general Turkish population was reported to be 3.65% (Tuncbilek *et al.*, 1999). Malformations occur with all of the commonly used anticonvulsant drugs. The possible mechanisms of teratogenicity include folic acid antagonism, fetal tissue binding, and toxic effects of metabolic intermediates (Yerby, 1987 ; Hosli *et al.*, 1999 ; Oguni and Osawa, 2004 ; Kampman, 2007). The congenital malformation rates in the PHT, CBZ, PB, and VPA monotherapies were higher than general population as expected. Rates of malformation in pregnancies in women with epilepsy were reported to be 5.3-17.7% (Robert *et al.*, 1986 ; Kaneko *et al.*, 1988 ; Wilhelm *et al.*, 1990 ; Kaneko *et al.*, 1992 ; Dravet *et al.*, 1992 ; Battino *et al.*, 1992 ; Garza-

Morales *et al.*, 1996 ; Sabers *et al.*, 1998). In our study, we found a malformation rate of 10% in infants of 80 pregnant women with epilepsy. Use of AEDs during pregnancy significantly increases the risk of congenital malformation in the offspring compared to the general Turkish population (10% versus 3.65%) ($p < 0.05$). The different preparations (mono or polytherapy) and doses of AEDs can be the cause of differences in literature for the congenital malformation rate.

Kanoke *et al.* showed that monotherapy versus polytherapy reduced malformation rates in pregnancies in women with epilepsy (1988). Valproate, phenytoin and phenobarbital were the most teratogenic drugs (Dravet *et al.*, 1992 ; Battino *et al.*, 1992 ; Sabers *et al.*, 1998). An overview has suggested that of the older first-line therapies, carbamazepine therapy carries slightly less risk compared to valproate, phenytoin, phenobarbitone or mysoline (Dansky, 1995). Our results showed the teratogenicity of different AEDs (CBZ, PHT, VPA and PB) resulted in different percentages for fetal malformations (PHT ; 14.28%, CBZ ; 6.52%, VPA ; 13.33% and PB 20%). We defined PB as the most and the CBZ as the least teratogenic. CBZ group was the largest patient group. 6.52% of pregnancies with CBZ monotherapy resulted in malformed babies. There was no statistically significant difference between CBZ group and the general Turkish population ($p > 0.05$).

Phenytoin in monotherapy has been associated with a pattern of malformations called the fetal hydantoin syndrome. This consists of pre-natal and post-natal growth deficiency, microcephaly and developmental delay, in combination with dysmorphic craniofacial abnormalities and nail and distal pharyngeal hypoplasia. Barbiturates in monotherapy have also been associated with congenital heart defects and facial clefts. Carbamazepine in monotherapy was associated with hip dislocation, inguinal hernia, hypospadias, congenital heart defects and neural tube defects (Bertollini *et al.*, 1987). Valproate appears to be only AED for which a dose-response relationship has been observed. A high daily dose above 1000 mg/day or a high peak dose appears to increase the risk of congenital malformations. Malformations associated with sodium valproate include neural tube defects (2.5%), craniofacial, skeletal, cardiovascular, urogenital and cerebral defects (Lindhout *et al.*, 1992 ; Vajda and Eadie, 2005).

Our study suggests that the rate of congenital malformations in infants of mothers with epilepsy is higher than that in the general Turkish population, but significant differences were not observed for the CBZ group. Large size controlled studies may lead to different conclusions.

The safest agents among the conventional AEDs need to be discussed along with the contradicting observations from other studies and the general

consensus. All conventional AEDs carry the risk of fetal malformation and the selection of AED should be guided by the epileptic syndrome and seizure type.

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