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Malformations in newborns associated to anticonvulsant consumption during pregnancy. Experience in third level hospital of Mexico

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ABSTRACT

Aim. The purpose of the present study is to determine the relationship between the anticonvulsant drug use during pregnancy and the presence of malformations in the newborns. **Methods.** The frequency of malformations in the neonates of epileptic mothers under anticonvulsant treatment was analyzed in two periods, one from 1988 to 1992, which included 76 epileptic mothers, and another from 1996 to 2003 with 170 patients. Results: In the first period, 51 (67.1%) of mothers received monotherapy and 25 (32.9%) received polytherapy of phenytoin with carbamazepine, valproic acid or phenobarbital. In this period, 4 newborns (16%) with congenital malformations were registered. In the second period, 159 (93.5%) of the epileptic mothers received monotherapy and 11 (6.5%) received polytherapy of valproic acid with carbamazepine or phenytoin. During this period only 3 newborns 27.3% with malformations were registered. **Discussion.** Clinical treatment should consider the risk of using polytherapy, mainly if phenytoin or valproic acid are combined with other anticonvulsants.

Key words. Anticonvulsants. Malformations. New borns. Pregnancy. Theratogenic.

Malformaciones en recién nacidos al consumo de anticonvulsivantes durante el embarazo. Experiencia en un hospital de tercer nivel de México

RESUMEN

Objetivo. *El objetivo del presente estudio es conocer la relación entre el consumo de anticonvulsivantes durante el embarazo y la presencia de malformaciones en los recién nacidos.* ***Métodos.*** *Se comparó la frecuencia de malformaciones en recién nacidos de madres epilépticas tratadas con anticonvulsivantes durantes dos periodos, uno de 1988 a 1992 con 76 casos y otro de 1996 a 2003 con 170.* ***Resultados.*** *Durante el primer periodo 51 pacientes (67.1%) recibieron monoterapia anticonvulsivante y 25 politerapia (32.9 %), usando fenitoina, carbamacepina, ácido valproico o fenobarbital. En este periodo cuatro recién nacidos de las pacientes tratadas con politerapia (16%) presentaron malformaciones. En el segundo periodo 159 pacientes epilépticas (93.5%) recibieron monoterapia y sólo 11 fueron tratadas con politerapia (6.5%), combinando ácido valproico con carbamacepina o fenitoína. Durante este periodo sólo tres recién nacidos presentaron malformaciones (27.3%), hijos de madres epilépticas tratados con politerapia.* ***Discusión.*** *El tratamiento con politerapia debe de considerar el estado clínico de las pacientes, ya que el uso combinado de los anticonvulsivantes condiciona la presencia de malformaciones congénitas.*

Palabras clave. *Anticonvulsivantes. Malformaciones. Recién nacidos. Embarazo. Teratogénico.*

INTRODUCTION

Pregnancy is considered of high risk when patients present hypertension, epilepsy, advanced age or diabetes mellitus, among other diseases. The epileptic woman is in greater risk of presenting convulsive crisis during pregnancy, labor and puerperium, which can damage the development of the fetus and the evolution of pregnancy, increasing the risk of an early interruption.[1-4] It has also been observed that body weight above 80 kg during pregnancy increases the relative risk of neural tube defects by 1.9%.[5,6] Another factor which can contribute to produce malformations is the use of drugs; most anticonvulsants are known to freely cross the placental and the hematoencephalic barrier. Some anticonvulsants have been shown to produce teratogenic effects and the combination of two or more anticonvulsants increases the risk of produce malformations, manifested as physical and anatomical abnormalities in the short term, and behavioral anomalies in the middle- and long term.[7-10]

Anticonvulsant drugs are divided into two groups, the older and the newer ones, according to their introduction before and after 1990. Carbamazepine, phenobarbital, phenytoin, primidone, etosuximide and valproic acid are among the drugs introduced before 1990, so a wide use has been made of them, and their effect of introducing an appreciable risk of congenital malformations, higher when combining two or more of these drugs, has been demonstrated as well. The general risk is about 4-6%.

New anticonvulsants are felbamate, gabapentin, lamotrigin, levetiracetam, oxcarbacepin, tiagabin, topiramate and zonisamide. Although lamotrigin and oxcarbacepin have been used in Europe and zonisamide in Japan during the last ten years, enough information relating to their safe use during pregnancy is still missing.

The informed number of exposed persons to these drugs is not reliable enough to determine malformation rates. These compounds were approved by the FDA to be used as a coadjuvant therapy, and their use during pregnancy is under a multiple drug schedule, so the observed adverse effects cannot be attributed solely to one of them.[7]

Major malformations are defined as structural abnormalities of surgical, medical, or esthetic importance, among which are included abnormal neural tube closure, cleft lip and palate, congenital cardiac anomaly and urogenital defects, which are present in 2 to 3% of the newborn population.[2,11-13]

The use of polytherapy conditions the appearance of the anticonvulsant syndrome in the fetus. These children present major malformations, delay of intrauterine growth, microcephalia and cognitive dysfunction[13]. Growth delay is considered when children are under 2,500 g of weight. This occurs in 7-10% of the population of epileptic mothers, treated mainly with valproic acid or carbamazepine monotherapy or with a combination of phenobarbital and phenytoin polytherapy.[13,14] Prevalence in Mexico of newborns with neural tube closure defects occurring between the third and fourth weeks of pregnancy is 3.26 per 1000 live births.[6] Carbamezepine and phenobarbital have been associated with folic acid deficiency, and valproic acid intervenes in the folate metabolism of epileptic mothers increasing the risk of defects in neural tube closure of live newborns.[13,15]

Women with high risk pregnancy due to epileptic seizures were attended at Instituto Nacional de Perinatología (INPer), in Mexico City, from 1988 to 2003, and the aim of the study was to determine the relationship between the use of anticonvulsant drugs during pregnancy and the risk of developing malformations in their living newborns.

MATERIAL AND METHODS

The present is a retrospective, descriptive study. Data for the study were collected from the medical history of patients attended at the service of hospitalization and at the Epilepsy Clinic at the INPer. First, this study brings information about what kind of anticonvulsant drugs are currently used in this institution to treat epileptic seizures in pregnant patients. Second, two periods were chosen to analyze the malformation frequency in newborns from epileptic mothers under anticonvulsant treatment, and were then compared. The first period covered from 1988 to 1992 with 76 epileptic patients. The second period covered from 1996 to 2003, and 170 patients were included.

Epileptic mothers

Patients included were between 18 and 40 years of age, with weight between 50 and 85 kg and with diagnosis of epilepsy without additional disease (epilepsy was defined as a lifetime history of at least two unprovoked seizures).[16] All patients were primigravidae, i.e. pregnant for the first time,[17] and received medical attention since the first trimester of pregnancy. All of the patients took polyvitamins since the first trimester of pregnancy, and their folic acid

administration was performed initially when the patients were included in the study, during the first week of pregnancy. As recommended, folic acid administration to pregnant women should be performed from the fourth week before conception and the end of the first trimester, in order to prevent the development of neural tube defects; however some health professionals suggest to administrate folic acid even before the pregnancy is started and to keep its use until the fourth week gestation is achieved (when the neural tube development is concluded). As the United States Public Health Service recommended in 1992, through its Center for Disease Control and Prevention (CDC), all of the women likely to be pregnant should take 0.4 mg per day of folic acid.[18,19] The anticonvulsant drugs were taken during the entire pregnancy period, since the patients were order to take them from the moment when epilepsy was diagnosed, which was an average 5-year period. No changes were necessary in patients treated with monotherapy since they were well controlled. Spontaneous abortions or stillborns detected during the two study periods were excluded. Spontaneous abortion was defined as fetal death before 20 weeks of gestational age and stillborn was defined as an infant dead at birth.[15]

Newborn

The newborn were examined by a physician, including height, weight, circumference and bitemporal width of the head, gender, Apgar score and gestational age. Apgar score was chosen as a simple and repeatable method to quickly and briefly assess the health of newborn children immediately after childbirth.

Classification of seizures

Patient's seizure semiology was obtained from the medical history based on specific aura, unilateral sings, and alteration of consciousness. Epileptic mothers were classified according to the international classification of the seizures as partial or generalized seizures.[16]

First period of study

In the first period, the profile of anticonvulsant drug consumption by epileptic mothers was taken from the drug supply control books at the hospital pharmacy and corroborated with medical records from the neurological attention department. Having gathered the patients' data, the period of pregnancy was followed-up to evaluate the health status and damage possibilities of the newborn, according to physical exploration and Apgar score.

Second period of study

By the time of the second period of the study, medical attention for epileptic mothers had been improved by the creation of the Epilepsy Clinic in which more specialized attention is given by gynecologists, neurologists, and pharmacologists.

A statistical record of all epileptic mothers is kept since the creation of the Epilepsy Clinic, which registers age, weight, weeks of pregnancy and type of crisis, as well as the doses of anticonvulsive drugs administered throughout pregnancy. Some clinical data were complemented with information obtained from the medical history, birth and the newborn health status.

Statistical analysis

Descriptive analysis of data was performed, but when treatments of populations from both periods was compared, significance was considered at $p < 0.05$ by using nominal square chi (χ^2).

RESULTS

Seventy-six epileptic patients were analyzed during the first period. Epileptic mothers with partial simple and tonic-clonic generalized seizures were treated with phenytoin monotherapy in 67.1% of the cases (interval of confidence, IC= 56.56-77.64). Polytherapy was used in 32.9% of the cases (IC= 22.36-43.44) (Figure 1) and the combinations were: phenytoin, carbamazepine and clonazepam (15.8%), phenytoin with carbamazepine (14.5%) and phenytoin with phenobarbital, carbamazepine and valproic acid (2.6%). All mothers treated with monotherapy had children with no malformations. In mothers treated with polytherapy, the risk of malformation increased in their newborns who presented anomalies in 4 cases (16%) probably as a function of the number of anticonvulsants administered (Table 1). As footnote appears the doses used during both phases.

Two mothers with partial seizures were treated with phenytoin plus carbamazepine. This combination caused ventricular septal defect or hydantoin syndrome in their newborns, one female of 41 weeks and one male of 39.1 weeks gestation, weighing 2600 and 2350 g and Apgar score 8/9 and 8/8, respectively.

Table 1. Demographic data of pregnant patients in the two periods of study

Study periods	Age (years)	Weight (kg)	Seizure type	Therapy Anticonvulsant
First period				
Case 1	22	55	Partial	PHT + CBZ
Case 2	36	62	Generalized tonic-clonic	PHT + CBZ + VPA+ PB
Case 3	22	81	Generalized tonic-clonic	PHT + Clonazepam+ CBZ
Case 4	23	53	Partial	PHT+ CBZ
Second period				
Case 1	36	65	Generalized tonic-clonic	VPA + PHT
Case 2	23	59	Absence	VPA + PHT
Case 3	21	69	Generalized secondary-partial	VPA + CBZ

PHT (Phenytoin) (300 mg per day), CBZ (Carbamazepine) (800 mg per day), VPA (Valproic acid) (15 mg/kg/day), PB (Phenobarbital) (100 mg per day). All patients took folic acid and polyvitamins since the first trimester of pregnancy. First period 1988-1992, second period 1996-2003.

Table 2. Demographic data of the newborn in the two periods of study.

Number of Case	Gender	Weight (g)	Apgar score	Gestational age (weeks)	Congenital malformation
First period					
1	F	2600	8/9	41	Ventricular septal defect
2	M	2500	8/9	39	Membranous ventricular septal defect, neural tube defect (non-specific) and unilateral cleft lip
3	F	3100	8/9	38.6	Ventricular septal defect
4	M	2350	8/8	39.1	Hydantoin syndrome
Second period					
1	F	3200	8/9	39.5	Ventricular septal defect
2	M	2800	8/9	38.5	Neural tube defect (non-specific) and coarctation of the aorta
3	F	2400	8/9	38	Lumbosacral spina bifida

First period 1988-1992, second period 1996-2003.

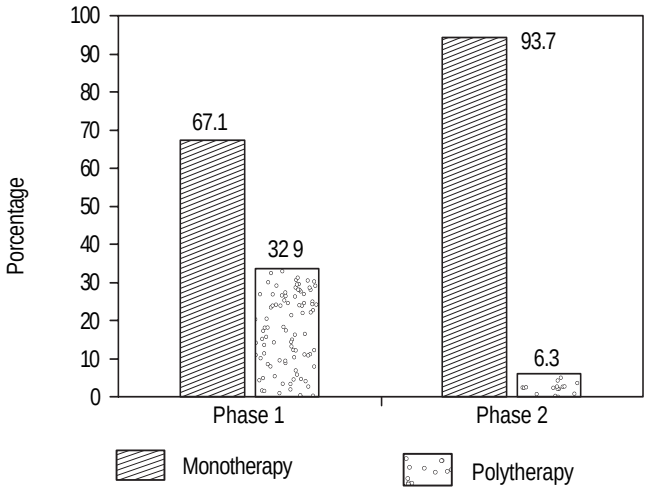

Figure 1. Percentage of anticonvulsants used during pregnancy in the two periods of study.

The combination of phenytoin plus phenobarbital, carbamazepine and valproic acid administered to mothers with generalized tonic-clonic seizures caused membranous ventricular septal, defects of neural tube closure (non-specific) and unilateral cleft lip in a newborn male of 39 weeks gestation, weight 2,500 g and Apgar score 8/9. Combined administration of phenytoin, carbamazepine and clonazepam to a mother with generalized tonic-clonic seizures, generated malformations in a newborn female of 38.6 weeks gestation, weight 3,100 g, Apgar score 8/9 and presence of ventricular septal defect (Table 2).

The second period of the study included 170 epileptic patients. Of these, 93.5% (IC= 89.8-97.2) received monotherapy; 65.9% with carbamazepine, 21.7% phenytoin and 5.9% valproic acid (Fig. 1). All epileptic mothers treated with only one drug had children with no malformations. The remaining

6.5% (IC = 2.8-10.2) of mothers required polytherapy, in the following combinations: carbamazepine with valproic acid in 3% of the cases administered to mothers with generalized secondary-partial seizures and phenytoin with valproic acid in 3.5% administered to mothers with generalized tonic-clonic and absence seizures. One mother who received the first combination, gave birth to a female infant of 38 weeks, 2,400 g weight and Apgar score 8/9 with lumbrosacral spina bifida. The combination phenytoin with valproic acid administered to two epileptic mothers caused ventricular septal defect, neural tube defect (non-specific) and coarctation of the aorta in their newborns, one female of 39.5 weeks and one male of 38.5 weeks gestation, weighing 3200 and 2,800 g, both with Apgar score of 8/9 (Table 2). Malformations were only observed in 3 cases (27.3 %), this could be attributable to the fact that three of the eleven patients who received combined therapy presented with an epileptic seizure during gestation. All epileptic patients in the second period of study were treated and monitored at Epilepsy Clinic. For phase 1, χ^2 was 8.89, p = 0.0029 gL 1 and for phase 2, χ^2 = 128.85 p < 0.0001 gL 1.

DISCUSSION

The presence of malformations in the patients studied here was partially due to the fact that they took anticonvulsants since the first trimester of pregnancy. The presence of malformations is associated to the use of polytherapy, and to the stage of pregnancy at which the drugs are administered.[13] The association between the use of anticonvulsants by epileptic women and congenital malformations has received rising attention.[20,21] Seventy percent of women with epilepsy have been well controlled with optimal anticonvulsant treatment, however, the remaining 30% shows a deficient response to treatment.[22]

In Mexico, one factor that has influenced abatement of the malformation index is the creation 13 years ago of the Epilepsy Clinic at INPer, where epileptic patients are presently attended. This Clinic keeps control of patients with studies that determine their type of epilepsy and can establish adequate treatment. Another fundamental factor has been the contribution of the Pharmacology Department at the same Institute, where patients are monitored and treatments are individualized.

With respect to the patterns of anticonvulsant, the most frequently prescribed was carbamazepine, probably for its well-known clinical and pharmacological advantages. Phenytoin, valproic acid and phenobarbital were used as a second to fourth option. Although new anticonvulsants have been available for one decade, they are probably not used during pregnancy because no studies have been made to determine their security and effectiveness.[13]

According with our results, the use of carbamazepine plus others anticonvulsants increases the frequency of malformations produced during gestation, and is associated with defects in neural tube closure,[23-27] and phenytoin in combination with 2 or more anticonvulsants is associated to the hydantoin syndrome.[21] These drugs comprise approximately two thirds of the anticonvulsants most frequently used at INPer.

Our results agree with reports in the literature, which describe that exposure to anticonvulsants during the first trimester, causes defects of neural tube closure, open spina bifida and anencephaly (32 days after conception), cardiac malformations such as defect of the atrial septum, defect of the ventricular septum, Fallot's tetralogy, aortal stenosis, persistence of the arterial conduct and pulmonary stenosis (days 21 to 56 after conception) and the development of cleft-lip and palate (days 42-63 after conception). Some of these disorders were observed in our study.[2,13,27]

We concluded that the establishment of a Clinic of Epilepsy within the INPer, improves the treatment of epileptic pregnant patients, since 90% of the attended women in the second phase were administered monotherapy, and only 6.5% of them required combined therapy (polytherapy) after an inadequate management of the seizures during pregnancy.

Care should be taken when combined therapy is to be performed, specially when using phenytoin, which increases the risk of developing malformations in newborns from epileptic women.

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