

# Pregnant Women with Epilepsy in a Developing Country

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**Abstract:** This is the first prospective study carried out in Argentina and Latin America to provide the impact of epilepsy throughout the childbearing years life of women, and pregnancy outcome in a population of pregnant women with diagnosis of epilepsy and antiepileptics drugs (AEDs). Ninety-four women were studied prospectively at the Epilepsy Center, the largest in Argentina. Of the 94 women examined in this study only 10% planned their pregnancy and received folic acid before conception.

More than half of women in our study were on monotherapy, with the most frequently prescribed drugs being carbamazepine and valproic acid. In all, 90.4% of the women had a normal pregnancy and delivery. There were 8.5% spontaneous abortions. Major congenital malformations (MCM) was detected in 10.6% of newborns at birth; in the general population it varies between 1.6-3.2%. The results from this study are helpful in the highlighting correct gaps in knowledge in this population group.

**Keywords:** Epilepsy, gender, women, pregnancy, AEDs, family planning, developing countries.

## 1. INTRODUCTION

Epilepsy is the most common serious neurological disorder and is one of the world's most prevalent non-transmissible diseases [1, 2]. Over four-fifths of the 50 million people diagnosed with epilepsy live in developing countries. People with epilepsy continue to be stigmatized and have a lower quality of life than people with other chronic illnesses. Epilepsy has different implications for life and well-being in men and women; a major concern is the care of women with epilepsy during pregnancy and throughout all phases of their reproductive life. A recent report from the World Health Organization on gender inequality in health indicates that women have increased exposure and vulnerability to risk and limited access to health care and information [3]. There is deficient evidence and data for the clinical care of female with epilepsy in Argentina and Latin America. In this context, the main purpose of this study was to investigate the impact of epilepsy throughout the childbearing years of women's lives and on pregnancy outcomes.

## 2. METHODS

### 2.1. Population

This investigation was performed at the Epilepsy Center of Ramos

Mejía Hospital (EC), which is the largest epilepsy center in Argentina. Patients are referred to the EC by neurology departments from different parts of the country; a minority of patients also attend the EC spontaneously.

The women admitted to this study were all examined by the same group of neurologists who diagnosed epilepsy and monitored the women throughout pregnancy and up to one-year post delivery.

All patients who participated in this study were asked to complete a self-questionnaire in order to gain more insight into gender-related aspects of family planning, contraceptive use and information about epilepsy and potential risks of antiepileptics drugs (AEDs) effects.

The study was conducted with the approval of the ethics committee of Ramos Mejía Hospital in accordance with the ethical standards of the 1964 Declaration of Helsinki. All participants submitted informed consent.

### 2.2. Patient Selection

Between December 2002 and June 2009, 129 women diagnosed with epilepsy and being treated with AEDs were admitted to the Epilepsy and Pregnancy outpatient clinic (EP) created in 2002. Since 2002, the EP has been advertising its activities at the Neurological National Congress, the Epilepsy Congress, on its website and through the mass media. EP advertisements were also present in the waiting room of the EC. These advertisements made it clear that patients could attend the EP without an appointment if they were pregnant or planning on becoming pregnant. Staff at the hospital's obstetric unit were also informed of EP activities.

In this study, 94 pregnant women taking AEDs at the time of conception were included prospectively according to the following criteria:

1. Female aged 18–40
2. Clinical diagnosis of epilepsy
3. AEDs treatment

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4. Confirmed pregnancy
5. Agreed to complete survey questionnaire
6. Follow-up every trimester until delivery

### 2.3. Diagnosis of Epilepsy

All patients included in this study underwent a complete clinical and neurological assessment of seizure semiology. Additional studies, including interictal EEG and MRI, were used to confirm the type of epilepsy, consistent with standardized medical procedures [4].

### 2.4. Diagnosis of Pregnancy

All women admitted to the EP were incorporated according to the prospective protocol EURAP, an international registry of Antiepileptic Drugs and Pregnancy [5]. Our EP is the national coordinator for EURAP. Most patients were referred to the EP by an epileptologist of the EC, while others came spontaneously in response to the advertising. EURAP protocol was adhered to from the beginning of the study. All aspects related to epilepsy, pregnancy, childbirth and the newborn (until one year of age), and clinical and AEDs impact were prospectively assessed. Information on

**Table 1. Self-Completed Questionnaire**

Questions:		Patients (Percentage)
1- Epilepsy, as a condition, can have an impact on the following (check all that apply):	0-None	
	1-Pregnancy	75 (80%)
	2-Your own health	-
	3- Baby's health	84 (90 %)
	4- Birth control	56 (60%)
2- Antiepileptic drugs, used to treat epilepsy, can have an impact on the following (check all that apply)	0-None	
	1-Pregnancy	40%
	2-Your own health	-
	3- Baby's health	84 (90%)
	4-Birth control	56 (60%)
3- What kind of birth control did you use?	5-Sexuality	-
	1-Barrier	10 (9%)
	2-Birth control pill	9 (8%)
	3-Other	
4- Did you plan your pregnancy?	4-None	75 (80%)
	1-Yes	9 (10%)
	2-No	85 (90%)
5- When was the first time you discussed family planning with your physician?	1-At first visit	
	2-After several visits	10 (10%)
	3-During pregnancy	47 (50%)
	4-Never	37 (40%)
6- Have you ever voluntarily terminated a pregnancy?	1-Yes	1 (1%)
	2-No	
7- Has your partner used any contraceptive methods?	1-Yes	56p (60%)
	2-No	38p (40%)
8- Are you employed?	1-Yes	28 p (30%)
	2-Housewives	55 p (58%)
	3- No	11 p (12%)
9- Are you married or living as married?	1-Yes	70 (75%)
	2-No	24 (25%)

patient demographics, type of epilepsy, seizure frequency, family history of malformations, drug therapy, AEDs (type and dose during the follow up), start date of folic acid (FA) supplementation, ultrasound examination, or other methods of amniocentesis and of other potential risk factors was recorded in the registry. Follow-up data were collected once each trimester, at birth and at one year after delivery and also recorded in the registry.

The attending neonatologist reported the abnormalities observed in the newborns. The final assessment and classification of the type of malformation was conducted by the central project commission of EURAP using EUROCAT coding [6, 7].

## 2.5. Gender Aspects

In order to assess qualitative aspects related to gender such as family planning, contraceptive use and information about epilepsy and potential risks of AEDs effects, we used a self-questionnaire that we had designed for this purpose (Table 1). The questionnaire also addressed aspects related to social life, marital status and employment. All the patients included in this study completed the survey.

## 2.6. Data Analysis

The Student's *t* test was used to compare quantitative variables, and Fisher's exact test was used to compare qualitative variables. Binary logistic regression was applied to qualitative variables, and the odds ratio (OR) and 95% confidence interval (95% CI) were determined. SPSS for Windows (version 10.0) was used for statistical analysis.

## 3. RESULTS

For this study, 94 pregnant women diagnosed with epilepsy who were receiving AEDs were selected and prospectively included between December 2002 and June 2009. An additional 7 patients were excluded due to ongoing pregnancy, and 28 women were not followed-up.

The survey (Table 1) indicated that 90% (n=85) of women studied had not planned their pregnancies; this rate is similar to that observed in the general population [9]. When asked, if patients used any contraceptive methods, 80% of patients (n=75) answered negatively; however, when asked if their partners used any contraceptive method, 60% of them (n=56) claimed they used barrier methods as a means of contraception. This apparent contradiction may be due to lack of information and sexual education. In relation to epilepsy, 90% of women (n=84) were concerned about their babies "health" and the toxic effects of AEDs that they were exposed during pregnancy. However, only one patient had history of a voluntarily interrupted pregnancy, probably because abortion is illegal in Argentina. Information about family planning was received by only 60% of patients (n=57), the most during pregnancy. In relation to employment, 30% (n=25) of patients were employed, 12% (n=11) were unemployed and the remaining patients described themselves as housewives.

In terms of education, 50% of patients (n=47) had reached a secondary school level, which is similar to the general population [8]. Regarding ethnicity, 68% (n=64) of patients were white, 25% (n=24) were of mixed descent

(asian and black) and 6% (n=6) were of indigenous origin (Table 2).

In relation to epilepsy, 70% of patients (n=66) had focal epilepsy, 24.4% (n=23) had generalized epilepsy and 5.5% (n=5) were unclassified (Table 2).

Seizure control during the second and third trimester was compared with that during the first trimester. It was observed that 55.3% of patients (n=52) maintained the same seizure frequency, 27.6% (n=26) improved and 17% (n=16) deteriorated; there was one case of non-convulsive status epilepticus related to a lowering of VPA dose. Forty-five percent of patients (n=43) were seizure free during the entire pregnancy (Table 2).

In regard to treatment, 65.9% (n=62) patients received monotherapy, 48.3% (n=30) were treated with carbamazepine (CBZ), the most frequently drug used, and 32.2% (n=20) were treated with valproic acid (VPA). In the group of patients receiving polytherapy, the most frequent drug combinations were VPA and benzodiazepines (BDZ), CBZ and phenobarbital (PHB), and CBZ and VPA. In total, 16% of patients (n=15) received "second-generation" AEDs (lamotrigine (LMT), topiramate (TPM), levetiracetam): 2 patients received these drugs as monotherapy, and 13 patients received them in polytherapy. Treatment remained unchanged in 54.2% of patients (n=51), was reduced in 28.7% of patients (n=27) who were free of seizures at the beginning of pregnancy, and was augmented in 17% of patients (n=16) who showed an increase in the frequency of seizures.

At the time of enrollment, 70% of patients (n=66) were in the 16th week of gestation, 25.5% (n=24) were in their second trimester and 4.4% of patients (n=4) were in their third trimester of gestation. Only 10% (n=9) received FA supplementation before conception. These women were admitted to EC for family planning, and the information included in the record of each patient. Fifty-five percent of patients (n=52) received FA during the first 16 weeks of pregnancy.

Ninety percent of patients (n=86) had normal pregnancies and deliveries. There were 8 patients who underwent spontaneous abortions. Of these 8 patients, 4 were receiving monotherapy with CBZ (1200 mg/d; 600 mg/d; 400 mg/d and 200 mg/d), 3 were receiving monotherapy with VPA (800 mg/d) and the remaining patient received polytherapy with LMT (450 mg/d) and clonazepam (CLZ) (2 mg/d). Of the 4 patients receiving CBZ monotherapy only 2 received FA.

In relation to prenatal diagnosis, no more than 59.6% of patients (n=56) underwent low-resolution ultrasound examination, which was normal in all the cases analysed. Only one patient was examined for chromosomal abnormalities.

Of the 86 births, there were two cases of perinatal death. One of the patients received polytherapy with CBZ (1000 mg/d) and TPM (200 mg/d), and the other one was treated with CLZ (2 mg/d). Neither of these patients received folic acid because their pregnancies were not planned. The causes of death were prematurity and bronchial aspiration, respectively. No autopsies were performed in either case.

MCMs were detected in 10.6% (n=9) of the newborns at birth. Ultrasounds had been conducted on 8 of the mothers from this group, all of which were normal. Of these 9 pa-

**Table 2. Demographic Data**

		Pat.	Percent
Ethnicity	White	64	68%
	Mixed Origin	24	25%
	Aboriginal	6	6%
Educational Level	Primary	33	35%
	Secondary	47	50%
	Tertiary	12	13%
	Below-primary	2	2%
Gestational age at admission	1st Trimester	66	70%
	2nd Trimester	24	24%
	3rd Trimester	4	5%
Type of Epilepsy	Focal	66	70%
	Generalized	23	24%
	Undetermined	5	5%
Seizure Control	Equal	52	55%
	Best	26	27%
	Worse	16	17%
Treatment Scheme	Monotherapy	60	64%
	Polytherapy	34	36%
Use of Folic Acid	before pregnancy	9	10%
	after pregnancy	85	90%

tients, 3 patients received monotherapy with VPA, 2 patients received monotherapy with CBZ, 2 patients received polytherapy with phenytoin and TPM, 1 patient received polytherapy with CBZ and TPM, and the final patient received polytherapy with CBZ and PHB. Two patients received FA. Of all live births, only 20 could be evaluated during the first year after birth. All were normal.

#### 4. CONCLUSIONS

This was the first prospective study carried out in Argentina and Latin America to provide qualitative information regarding gender issues in a population of pregnant women with diagnosis of epilepsy and receiving AEDs.

Ninety-four pregnant women with a diagnosis of epilepsy receiving AEDs were studied prospectively between December 2002 and June 2009 according to the EURAP protocol, an international registry of Antiepileptic Drugs and Pregnancy [5]. Although we attempted to provide access to our facility to women who were pregnant or planning on becoming pregnant, we found it very difficult to recruit this population, and the reasons for this difficulty remain unclear. A key reason for this may be due to fears the mother may have had for the health of her baby. As evidenced by the responses to the questions in our survey, many female EC patients discontinued the use of AEDs while they were pregnant, and they returned to EC after delivery. Another cause may be a feeling of guilt on the part of the mother for not having planned the pregnancy. Responses to the questionnaire indicated that most women were primarily concerned about the babies

"health" once they learned of their pregnancy; however, only 10% planned their pregnancy, and only one patient reported the voluntary termination of a pregnancy. The results from this study are applicable to other non-epileptic inhabitants of Argentina, particularly those in the lower income population, more than 60% of whom visit the hospital. Other factors likely to contribute to these findings are the illegality of abortion, the fairly recent implementation of family planning programs and fact that only a little more than half of the women talked to their neurologist and preconception counseling and received information during pregnancy. In relation to epilepsy, most patients presented with partial seizures, as our population in EC [4]. Nearly half of women were seizure free during the entire pregnancy, and seizure frequency did not change during pregnancy. There was one case of non-convulsive status epilepticus due to the lowering of AED. The seizure frequency is similar to other reports [10-13]. In regard to treatment, more than half of women were on monotherapy, with CBZ being the most frequently drug used, followed by VPA, while 77% received monotherapy [7]. The most common combinations in the group receiving polytherapy were VPA and BDZ, and CBZ and PHB. Sixteen percent of patients received second-generation AEDs, which is similar percentage to the general population of EC. The limited use is probably due to their high cost, not to special considerations for pregnancy.

In relation to pregnancy at the time of enrollment, only 10% of patients had planned their pregnancy and received FA supplementation before conception. Seventy percent of women were in the 16th week of gestation or less. More than

half of women received FA during the first 16 weeks of pregnancy. A survey conducted on 700 women at childbearing age in four hospitals in Buenos Aires showed that 90% were unaware of the beneficial effects of FA and did not plan their pregnancy [14, 15]. In other reports the most of women received FA before of pregnancy [16, 17]

In all, 90.4% of women had a normal pregnancy and delivery, analogous to other works [10, 11, 12, 17]. There were 8.5% spontaneous abortions. No conclusions can be drawn based on this small sample size, but it is similar to reports from the general population in Argentina [18]. This found it is slight increased in relation to Eurap report [10].

Prenatal diagnosis was normal in all cases, although only 59.6% of patients had an ultrasound examination; all scans were conducted on low resolution equipment. A number of different investigations showed that is essential to have the appropriate ultrasound equipment for detection of MCM [19].

MCM was detected in 10.6% (n=9) of newborns at birth, and ultrasounds were conducted on 8 mothers in this group. In the series of EURAP, almost 19% of cases with MCM were detected by ultrasound examination [10]. According to data from the Latin American Collaborative Study of Congenital Malformations [20], the MCM rates in the general population vary between 1.6-3.2%. The EURAP registry reported a total malformations rate of 5.7%. This outcome will be assessed in relation to exposure to individual drugs or drugs combinations only after sufficient data are available for a meaningful statistical analysis.

Of the 86 live births, there were two cases of perinatal death, neither of which could be related to the presence of MCM. In Argentina the neonatal death rate in 2007 was at 8.5 per 1000 healthy live births, almost double the figure found in countries throughout Europe and North America. [18].

Although the sample is small, given that the EC is the largest epilepsy center in our country and receives patients from different parts of the nation, we feel it can be considered representative of the behavior of women in Argentina, especially the low-income population.

The results from this study provide important information regarding the impact of epilepsy in women who are pregnant or childbearing age women and are helpful in the highlighting correct gaps in knowledge in this particular population group.

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