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Outcomes of pregnant women with refractory epilepsy

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ABSTRACT

Purpose: Epilepsy is the most common neurological disorder requiring medical treatment during pregnancy. However, very few studies are specially dedicated to pregnant women with refractory epilepsy. This study was carried out with the aim of describing obstetrical and neurological outcomes of pregnant women with refractory epilepsy in Brazil.

Methods: Pregnant women with refractory epilepsy were enrolled in longitudinal cohort study between January 2005 and January 2018. They were regularly followed by a neurologist until the end of pregnancy. Neurological outcomes included seizure control, status epilepticus and adherence to antiepileptic medications. Obstetrical outcomes included major congenital malformations and obstetrical complications.

Results: A total of eighty two patients with a mean age of 24.5 ± 5.5 were included in our study. A significant number of women experienced an increase in seizure frequency and the prevalence of status epilepticus was 8.5%. More than half were non-adherent to antiepileptic drugs. Most of patients required treatment changes during pregnancy, in dose and/or in number of antiepileptic drugs. Cesarean section was the preferred way of delivery and five cases of major congenital malformations were detected. Obstetrical complications were significantly associated with polytherapy, multiple comorbidities, poor adherence to treatment and seizure deterioration during pregnancy ($p < 0.05$).

Conclusions: Women with refractory epilepsy can have a significant risk of obstetric and neurological complications during pregnancy. Treatment of refractory epilepsy in pregnancy is a real challenge for neurologists.

1. Introduction

Epilepsy is a common neurological disorder characterized by recurrent seizures. Approximately 40% of women suffering with epilepsy are in the reproductive age group. Between 0.3% and 0.7% of all pregnancies are in women with epilepsy. It is the most common neurological disorder requiring medical treatment during pregnancy [1,2]. Epilepsy treatment presents important clinical challenges during pregnancy. Infants of women with epilepsy have an increased risk of congenital malformations due mainly to the teratogenic effect of anti-epileptic drugs (AEDs) [3]. Conversely, epilepsy itself and uncontrolled seizures may have an important role in the occurrence of other adverse obstetric outcomes [4]. Uncontrolled seizures during pregnancy have been associated with fetal loss, fetal hypoxia, and poor neurodevelopment as well [5]. Therefore, the treatment of women with epilepsy prior and during pregnancy is a challenge. Neurologists need to balance between maintaining an effective treatment regimen to the mother and at the same time avoiding the teratogenic risk of the medications [6].

Recent studies show that most of the pregnancies of women with epilepsy (WWE) remain seizure-free under contemporary methods of management [7]. Current data suggests that the majority of WWE have well-controlled seizures during pregnancy or have no change in seizure frequency. In addition, seizure control is obtained with monotherapy in the vast majority of the patients [8]. Nevertheless, drug-resistant epilepsy affects 30–40% of people with epilepsy [9]. Such patients are generally advised to wait with conception until seizure control has been achieved but there is a lack of evidence regarding the management of these patients if they become pregnant. Indeed, no previous study was specially dedicated to pregnant women with refractory epilepsy. Most of the previously published cohorts do not include patients with epilepsy from low- and middle-income countries, which may also impair the accuracy and the precision of these studies [10]. Strict evidence is lacking regarding refractory epilepsy management during pregnancy.

This study was conducted with the aim of describing adverse outcomes and seizure control of pregnant women with refractory epilepsy in Brazil.

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2. Methods

2.1. Study design and selection of cohort

We carried out a longitudinal cohort study composed of consecutive pregnant women who were under regular clinical follow-up in an outpatient clinic of refractory epilepsy of a university-affiliated, tertiary referral hospital in São Paulo, Brazil, between January 2005 and January 2018. All women with refractory epilepsy exposed to antiepileptic drugs at the time of conception were eligible for entry in the study. Refractory epilepsy was defined as when treatment fails to achieve seizure freedom for 12 months or more, for whatever reason [11]. Only patients who were already being followed up for at least 6 months prior to the diagnosis of pregnancy were included. Baseline period was set at 1 month before pregnancy for all patients. They were followed until 1 month after the delivery and the outcomes regarding pregnancy and epilepsy evolution were prospectively recorded throughout the follow-up. A standardized protocol guided the data collection for register. During pregnancy, data should be reported twice per trimester during the first and second trimester and thrice during the third trimester. Deadlines were stipulated as one week before completion of each trimester of pregnancy. Cases in which pregnancy outcomes were unavailable or lost to follow-up were excluded. The study was approved by the local ethics committee and complied with the principles cited in the Declaration of Helsinki.

We excluded from the current analysis retrospectively identified pregnancies, those occurring in women without epilepsy, those for which physicians did not submit reports within preset deadlines, and those for which follow-up was not yet completed at the current census. We also excluded pregnancies in which antiepileptic drugs were switched or withdrawn during the first trimester, those exposed to other potentially teratogenic drugs, and those with comorbidities associated with teratogenic risks

2.2. Index evaluation of subjects

Baseline data were retrospectively collected through medical records and clinical interview. We obtained information on patient's demographics, habits (eg. alcohol use, cigarette smoking and use of ilicit drugs), medical conditions, folic acid supplement (folate supplementation was arbitrarily deemed appropriate if started at least 3 months before conception and maintained throughout the first trimester irrespective of dose), use of other medications, family history, type of epilepsy, seizure frequency, family history of malformations, drug therapy and other potential risk factors. Information on previous pregnancies, deliveries, and fetal loss was also available. We classified seizures in accordance with the new operational classification proposed by the International League Against Epilepsy in 2017. Antiepileptic drug therapy was described as well as if the patient was in monotherapy or in polytherapy. Monotherapy was defined as exposure to only 1 anticonvulsant drug during the gestation and polytherapy was defined as exposure to 2 or more anticonvulsant drugs simultaneously at any time during pregnancy.

2.3. Outcomes

We prospectively collected through medical consultations and phone interview data regarding epilepsy and pregnancy outcomes during the follow-up period. We determined the natural course of epilepsy during pregnancy, including types of epilepsy, types and dosage variation of AEDs used to control the disorder, activity of epilepsy prior to conception, the presence of and frequency of seizures during pregnancy. Seizure frequency variation was quantified separately into one of four predefined categories (no seizures, increased number of seizures, decreased number of seizure and no variation). Seizure control was defined as achieving seizure freedom or presenting a significant reduction in seizure frequency (more than 50%) sustained for at least 3 months. In the same way, adjustment of the antiepileptic therapy during pregnancy was registered according to other four predefined groups (addition of another AED, withdrawal of an AED, replacement of and AED and no adjustment). Occurrence of status epilepticus was recorded as well. During follow-up, adherence to antiepileptic treatment was measured with Morisky Medication Adherence Scale (MMAS-8). MMAS-8 is a self-report questionnaire that is commonly used in epilepsy clinics [12] and it has already been validated against more definitive data such as plasma drug levels and medication possession ratio [13]. Total scores range from 0 to 8 and patients were considered adherent with scores greater than 6.

Primary obstetrical outcomes included the rates and the type of major congenital malformations (MCM) as documented at discharge from the maternity unit. A major malformation was defined as a structural abnormality with surgical, medical, or cosmetic importance. The physical features excluded were minor anomalies, birth marks, deformations, anatomic findings by ultrasound studies in pregnancy that were not identified by the examining pediatrician, complications of prematurity, genetic and chromosomal disorders. Only children born after diagnosis of maternal epilepsy and born during the study period were included in the analyses. The secondary obstetrical outcomes included spontaneous abortion (miscarriage at < 20 weeks of gestation), preterm birth (delivery before 37 complete weeks of gestation), mode of delivery and the incidence of other adverse pregnancy complications (induction of labor, cesarean section, antepartum hemorrhage, postpartum hemorrhage). We excluded cases of abortions induced for clear specific causes other than epilepsy and pregnancies in which fetal outcome could not be determined.

2.4. Statistical analysis

The data obtained was analyzed using a Student's *t*-test for continuous data (expressed as mean ± standard deviation) and a chi-square test for categorical data (expressed as a percentage). Comparisons of the rates of various adverse outcomes between both groups were performed, using Person's chi-squared test and a relative risk with 95% confidence interval. Final values were adjusted for potential confounders (eg. comorbidities, maternal age). P-value < 0.05 was considered significant. The statistical procedures were performed using SPSS version 22.0 (IBM Corp. 2012)

3. Results

From January 2005 to January 2018, 443 women with refractory epilepsy were followed up in our specialized outpatient clinic. Among them, we enrolled 124 patients who became pregnant and fulfilled the inclusion criteria for our cohort. Subsequently, 42 patients were excluded resulting in 82 eligible pregnancies (Fig. 1). The mean age was 24.5 (SD 5.5) and 36 and 13 patients had previous pregnancies and abortions, respectively. None of the women had exposure to other teratogens except AEDs. Carbamazepine was the most common antiepileptic drug used, followed by phenobarbital (48.8%), valproate (25.6%), phenytoin (9.8%), clonazepam (7.3%), clobazam (7.3%), topiramate (2.4%), lamotrigine (2.4%), oxcarbazepine (1.2%). First-generation antiepileptic drugs were the choice for the majority of patients (92.7%). Half of the subjects required polytherapy and 12 (29.3) of them took valproate. There were no drug changes during the baseline period. Poor adherence to treatment was registered in 42 (51.2%) patients. Folic acid was being appropriately used in 90.2%. Detailed baseline characteristics are presented in Table 1.

The AED dose was increased from the first to the third trimester in 50.0% of pregnancies (41/82). Another AED was added in 20 pregnancies. Treatment changes are summarized in Fig. 2.

At baseline, the median seizure frequency was 6 per month, ranging from 1 to 16. Concerning the frequency of seizure types, there was on

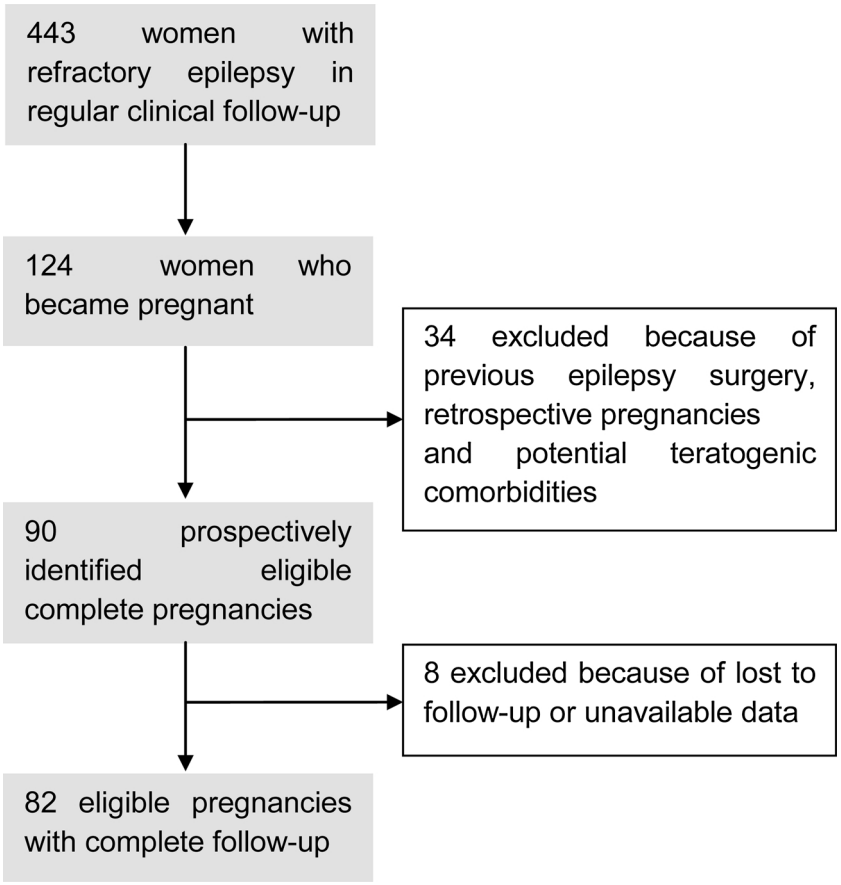

Fig. 1. Study population and flowchart selection.

Table 1
Demographic and clinical characteristics of the study population.

Age (mean, standard deviation)	24.5 (5.5)
Comorbidities	25 (30.5)
Alcohol consumption	2 (2.4)
Tobacco use	9 (11.0)
Monotherapy	41 (50.0)
Polytherapy	40 (48.8)
2 AEDs	34 (41.5)
3 AEDs	6 (7.3)
Folate	74 (90.2)
Previous pregnancies	36 (43.9)
1	25 (30.5)
2	6 (7.3)
3	3 (3.7)
4	2 (2.4)
Abortion	13 (15.9)
Etiology	
Unknown	29 (35.4)
Structural	38 (46.3)
Genetic	15 (18.3)
Seizure type	
Focal onset with impaired awareness	32 (39.0)
Focal onset aware	25 (30.5)
Focal to bilateral tonic-clonic	23 (28.0)
Generalized	31 (37.8)

average 5.2 generalized seizures per month and 7.8 focal onset seizures per month. Seizure control was obtained for 55 (67.1%) patients and it was statistically associated ($p < 0.05$) with good adherence, no dose adjustment during pregnancy and withdrawal of one antiepileptic drug (Table 2). Only 3 (3.6%) patients remained seizure-free during entire pregnancy. Patients who experienced an increase in seizure frequency were more likely ($p < 0.05$) to have had poor adherence to treatment, increased dose during pregnancy and need to add another antiepileptic drug. Increased seizure frequency was at the expense of focal onset seizures (69.1%). No association was observed between seizure frequency during pregnancy and etiology, comorbidities, polytherapy and type of antiepileptic drug. Detailed analysis of potential risk factors for worse neurological outcomes is reported in Table 2.

Status epilepticus occurred in 7 women (8.5%) with a mean age of 28.3 (SD 7.1) years. These cases were evenly distributed over the three trimesters. All cases were generalized tonic-clonic and 4 (57.1%) of them had already experienced SE before. The mean seizure frequency was 10.9 per month. There were no maternal or fetal fatalities. Increased number of AEDs used, use of 2.o generation antiepileptic drug, poor adherence to treatment and uncontrolled epilepsy during pregnancy were associated with increased odds of status epilepticus ($p < 0.05$). Concerning obstetric outcomes, status was significantly associated with cesarean delivery, obstetrical complications, prematurity and previous history of miscarriages ($p < 0.05$). Individual cases are reported in Table 3.

Cesarean section was the preferred way of delivery (51.2%) and it was correlated in our cohort to increased frequency of seizures and poor control of epilepsy during pregnancy ($p < 0.05$). Obstetric complications and pre-term births were reported in 24 (29.3%) and 21 (25.6%) cases, respectively. The incidence of obstetric complications was significantly higher in some conditions: polytherapy, multiple comorbidities, poor adherence to treatment, unsuccessful epilepsy control and increased frequency of seizures during pregnancy ($p < 0.05$). There was no registered abortion during follow-up. In our cohort, 5 (6.0%) fetal malformations were reported: 1 cleft palate, 1 ventricular septal defect, 2 myelomeningoceles, and 1 genitourinary malformation. Among these cases, 4 (80%) were born after maternal polytherapy and both cases of neural tube defects were born to mothers taking valproate

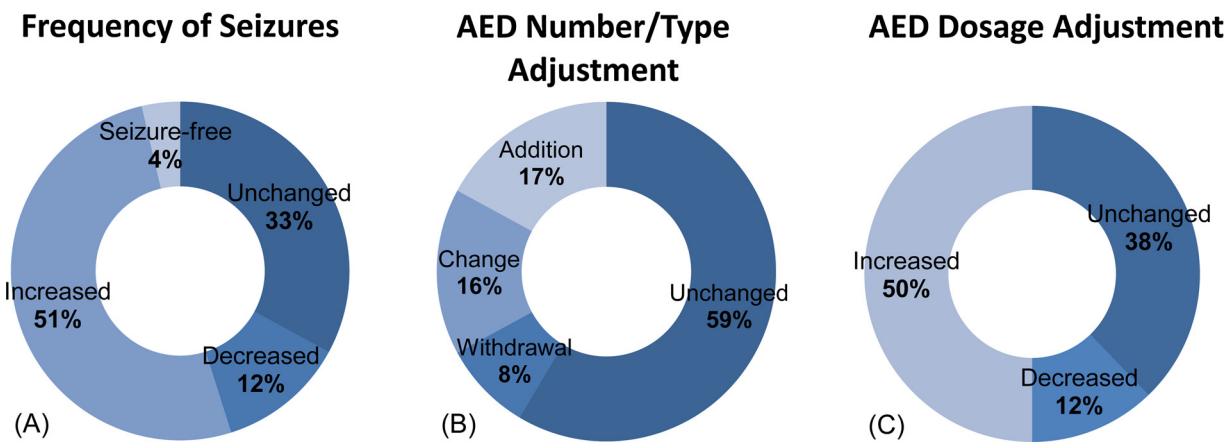

Fig. 2. Number (in %) of epileptic women according to frequency of seizures (A), antiepileptic (AED) number/type adjustment (B) and AED dosage adjustment (C) during pregnancy.

Table 2
Analysis of clinical characteristics and treatment information with seizure control and seizure frequency during pregnancy. Data are expressed in Odds Ratio (95% Confidence Interval).

	Seizure control OR (95% CI)	p-value	Increased frequency OR (95% CI)	p-value	Same frequency OR (95% CI)	p-value
Etiology	1.1 (0.4 – 2.8)	0.9	0.7 (0.3 – 1.7)	0.6	0.4 (0.1-1.2)	0.19
Polytherapy	0.8 (0.3 – 2.1)	0.8	2.0 (0.8 – 4.8)	0.18	0.6 (0.2 – 1.5)	0.4
Adherence	5.0 (1.8 – 13.8)	0.003	0.1 (0.03 – 0.2)	< 0.001	7.7 (2.5 – 23.4)	< 0.001
Dose adjusment						
None	3.9 (1.5 – 10.2)	0.007	0.6 (0.2 – 1.6)	0.05	1.2 (0.4 – 3.0)	0.8
Reduction	5.0 (0.6 – 42.4)	0.19	0.08 (0.01 – 0.69)	0.01	3.6 (0.9 – 14.2)	0.1
Increase	0.7 (0.2 – 1.8)	0.6	3.3 (1.3 – 8.2)	0.01	0.4 (0.1 – 1.1)	0.1
AED adjustment (number)						
None	2.3 (0.9 – 6.0)	0.11	0.7 (0.3 – 1.7)	0.6	1.0 (0.4 – 2.6)	0.8
Withdrawal	11.3 (1.2 – 99.0)	0.02	0.1 (0.01 – 1.2)	0.09	1.1 (0.3 – 4.4)	0.9
Change	0.7 (0.2 – 2.5)	0.8	1.1 (0.3 – 3.7)	0.9	0.8 (0.2 – 3.1)	0.8
Addition	0.8 (0.1 – 3.6)	0.9	4.3 (1.1 – 17.1)	0.01	0.5 (0.1 – 1.9)	0.4
Comorbidities	0.8 (0.3 – 2.2)	0.8	0.3 (0.1 – 0.9)	0.07	2.5 (0.8 – 7.6)	0.16
2.o generation AED	0.7 (0.1 – 4.5)	0.8	1.4 (0.2 – 9.2)	0.95	1.3 (0.2 – 8.8)	0.88
Valproate	0.5 (0.2 – 1.5)	0.3	1.7 (0.6 – 4.9)	0.3	0.5 (0.1 – 1.7)	0.4

(500 mg per day, both). Outcomes were not significantly different when comparisons were made between women taking different AEDs with different dosages. A multivariate analysis of potential predictors for harmful obstetrical outcomes is expressed in Table 4.

4. Discussion

Undoubtedly, epilepsy treatment in women who became pregnant is an important issue in Neurology. Most of previous observational studies regarding epilepsy and pregnancy usually included patients with different levels of epilepsy severity, ranging from those more benign to those considered refractory. So much so that many patients were without any AED during pregnancy in some studies. In other ones, just patients on monotherapy were included [14,15]. Therefore, refractory patients became easily excluded from current knowledge about management of epileptic women in pregnancy. However, the discussion of risks and benefits while treating refractory epilepsy during pregnancy is even more challenging. Moreover, most of data concerning the treatment of epilepsy in pregnancy provides from studies performed in developed countries settings, what may compromise the evidence of the results at a global level [16]. To our knowledge, this is the first study that characterizes obstetric and neurological outcomes of patients with refractory epilepsy.

Patients with refractory epilepsy may have poor seizure control

Table 3
Individual characteristics and outcomes of patients who experienced SE during pregnancy.

Age	Comorbidities	Previous history of miscarriages	Seizure type	Etiology	Polytherapy	Vaginal delivery	Obstetrical complications	Prematurity	Adherence
34	None	Yes	Focal	Structural	Yes	No	Yes	Yes	No
31	Hypertension/ Diabetes	No	Focal	Structural	Yes	No	Yes	Yes	No
22	None	Yes	Focal/ Generalized	Unknown	Yes	Yes	No	No	
26	None	No	Generalized	Unknwon	No	No	Yes	Yes	No
20	Hipothyroidism	No	Focal	Unknwon	Yes	No	Yes	Yes	No
40	None	Yes	Focal	Structural	No	No	No	No	No
25	Valvopathy	No	Focal to bilateral tonic-clonic	Structural	Yes	No	Yes	No	No

Table 4
Analysis of clinical variables associated with pregnancy outcomes. Data are expressed in Odds Ratio (95% Confidence Interval).

	Malformations OR (95% CI)	p-value	Obstetric complications OR (95% CI)	p-value	Prematurity OR (95% CI)	p-value	Cesaerean OR (95% CI)	p-value
Etiology	3.2 (0.4 – 21.6)	0.4	0.4 (0.1 – 1.2)	0.2	0.6 (1.2 – 1.9)	0.6	1.2 (0.5 – 3.1)	0.76
Adherence	4.1 (0.4 – 38.4)	0.4	0.3 (0.1 – 0.9)	0.06	0.6 (0.2 – 1.7)	0.5	0.5 (0.2 – 1.2)	0.18
Polytherapy	4.5 (0.4 – 42.6)	0.3	2.8 (1.1 – 7.6)	0.06	2.6 (0.9 – 7.6)	0.09	1.3 (0.5 – 3.2)	0.6
Valproate	2.0 (0.3 – 13.1)	0.8	2.3 (0.8 – 6.5)	0.1	3. (1.1 – 8.9)	0.07	1.7 (0.6 – 4.9)	0.3
Comorbidities	0.5 (0.05 – 5.2)	0.9	4.5 (1.6 – 12.6)	0.006	0.5 (0.1 – 1.4)	0.3	2.1 (0.8 – 5.5)	0.19
Seizure control during pregnancy	0.7 (0.1 – 4.5)	0.8	0.2 (0.07 -0.5)	0.004	0.2 (0.08 – 0.7)	0.01	0.1 (0.06 – 0.5)	0.002
Increased seizures frequency	0.6 (0.09 – 3.8)	0.9	3.2 (1.1 – 8.9)	0.04	1.7 (0.6 – 4.9)	0.3	3.7 (1.5 – 9.2)	0.008

during pregnancy. Previous studies showed that epilepsy in general tend to present a benign pattern during pregnancy [17]. According to the EURAP study data (2013), which included 3806 pregnancies in 3451 WWE, the frequency of seizures during pregnancy increased in 15.8%, decreased in 12.0%, and did not change in 70.5% women [7]. A review of 27 studies that included 2165 pregnancies in WWE confirmed that most of the patients with epilepsy did not have an increase in seizure frequency (75.9%) and on the other hand, 22.7% of them experienced a decrease in seizure occurrence [2]. Patients usually remain seizure-free during pregnancy according to several cohorts from different countries (30.8–73.6%) [18,19]. However, in our cohort of refractory patients, more than half had an increase in the frequency of seizures and only one third did not change the frequency. In addition, seizure freedom was observed in only 4% of our cohort. These findings are in line with previous studies who suggested that achieving seizure freedom or at least seizure control 1-year before conception is a good predictor of presenting a favorable behavior of epilepsy during pregnancy [18,20]. Another explanation can naturally come from the refractory nature of epilepsy that persists throughout gestation. During pregnancy itself, there may be an exacerbation of seizures due to several mechanisms such as AED pharmacokinetics, hormonal changes, and psychological and behavioral changes like sleep deprivation [21,22]. Therefore, patients who present a difficult seizure control prior to conception represent a specific risk group during pregnancy, since the risk that the frequency of seizures worsen may be greater and underestimated [23]. Neurological outcomes were not associated with type of seizure, etiology of epilepsy or clinical characteristics. Some studies suggested that epilepsy prognosis throughout pregnancy could vary depending on if crises were or focal or generalized. However, this data is still not so clear and considering that in our study the fact that epilepsy was always refractory to treatment by itself, it could statistically minimize the impact of more subtle clinical predictors, like epilepsy features.

In our study, most of patients required dose adjustment. Pregnancy may reduce plasma concentrations of AEDs, and therefore, any dose adjustment that is required, usually involves increasing the concentration of AEDs as the pregnancy progresses [7,24]. Nevertheless, we found that if AED doses were unchanged, seizure control was statistically more likely to be achieved. In a previous study of 74 pregnant patients whose dosages were not modified, seizure frequency was unchanged in 80% [25]. The fact that increases in doses and/or number of AEDs were more common in pregnancies with seizures may suggest that treatment changes in many cases were reactive to seizures, rather than being made proactively to prevent seizure deterioration [19]. Similarly, the fact that decreases in doses and/or number of AEDs were associated with higher odds of reducing seizure frequency and achieving seizure control reveals that neurologists are inclined to minimize the risks of antiepileptic medication in patients who might show a clinical improvement [7,22]. These results demonstrate the complexity of managing antiepileptic therapy during pregnancy in drug resistant epilepsy [26]. No differences were found in neurological outcomes considering AED type and combination therapy. Definitely, our data suggest that there might be scope for a more proactive approach in comparing different antiepileptic medications in larger prospective studies. In fact, no previous study was dedicated to compare treatment in refractory epilepsy in pregnancy.

Adherence was an important predictor of patient's clinical outcome in our study. More than half of women had a less than desirable adherence in our study. Moreover, a poor compliance to treatment was associated with increased odds of having uncontrolled seizures and obstetric complications. There is scarcity of published information regarding adherence to antiepileptic drugs during pregnancy. Adherence rates tended to be higher for WWE in these studies because it generally included patients with well controlled seizures, most of them achieving seizure freedom and with less comorbidities (the opposite of the characteristics of our cohort) [27,28]. Several reasons have already been described to influence adherence to epilepsy treatment. Misinformation, low educational level, perceived stigma, poor social support and subestimation of the importance of medications could have easily contributed to the results. Women have concerns regarding the effect of epilepsy and its treatment on motherhood. Pregnancy itself has already been associated with an increased risk for non-compliance to pharmacological therapy as well. Furthermore, seizure frequency, seizure control status and long time using AEDs were already associated with treatment non-adherence [27–29]. Our study suggests that ensuring the patient is taking the medication correctly may be an important and "easy" measure to adopt concerning epilepsy prognosis, perhaps even before considering more complex decisions, like changing the dose or the number of drugs.

Status Epilepticus (SE) is a major issue in pregnant women with refractory epilepsy. By contrast, there is a dearth of literature available on SE occurring in pregnancy over world, with majority being from obstetric centers. SE is prevalent in 0.6% of all pregnancies. Lu et al. reported pregnancy-associated SE as 2.1% of all cases of SE and in a recent cohort study, Rajiv et al. found that SE in pregnancy accounted for 5% of all SE [30,31]. Our prevalence rate was higher compared to those few previous studies as our cohort only included drug-resistant epilepsy cases. Poor control of seizures during pregnancy and low compliance to treatment were significantly associated with SE. This finding is consistent with the main risk factors for SE in general population [19,32]. Maternal and fetal outcomes were influenced by the occurrence of SE. Few previous studies that analyzed SE in pregnancy showed this trend to poor obstetrical outcomes [2]. No stillbirth or maternal mortality were related to SE. These data confirm previous observations [7,8] and are in contrast with earlier investigations, which were probably affected by reporting bias, suggesting high rates of maternal and fetal mortality in SE during pregnancy. We found an association between use of second generation AEDs and SE. This finding should be confirmed in a larger study but a possible reason is that in these cases epilepsy has been more difficult to control so that more drugs have been tried.

We observed a high prevalence of prematurity and obstetrical complications in our cohort of patients and, actually, this finding is consistent with other published studies [33,34]. In 2015, a systematic review identified 38 studies (2 837 325 women) examining pregnancy and reproductive outcomes in relation to epilepsy and pregnancy [35].

In WWE compared with women without epilepsy, the odds of spontaneous miscarriage, antepartum haemorrhage, hypertensive disorders, induction of labour, caesarean section, any preterm delivery and postpartum haemorrhage were increased [35–37]. However, no previous study specially assessed maternal and fetal outcomes in refractory epilepsy and therefore, our results show impressive rates of obstetrical outcomes compared to literature. Many previous cohorts failed to show an increased risk of such complications [2,35]. We found a statically significant association between seizure control and seizure frequency during pregnancy with obstetrical complications and pre-term births. Adherence to treatment, polytherapy and the presence of multiple comorbities were significantly associated with worse obstetrical outcomes. Polytherapy, regardless of AED type, was previously demonstrated to be harmful concerning these outcomes [38]. No differences were noted considering epilepsy etiology, seizures and AEDs types. No fetal death was detected in our study and in fact and therefore data are inadequate to support or refute an increased risk of miscarriage in WWE.

More than half of patients underwent cesarean delivery. An underlying cause includes the increased obstetrical and neurological complications risk due to refractory epilepsy [35,37,39]. Indeed, in or study, non-controlled seizures and increased seizures frequency were associated with higher odds of cesarean section. Another explanation may come from the lack of intimacy of obstetricians with epileptic patients, especially regarding the indication of the way of delivery. Comparing to the women in general, in Brazil, cesarean rates are variable but markedly elevated: in some regions, it can reaches the prevalence of 53% [40]. The American Academy of Neurology recommendations have suggested a probable increase in the rates of caesarean section in women exposed to AEDs. However, there is still no evidence on the optimal timing and mode of delivery in WWE [1,33,35].

We found a high prevalence of congenital malformations in our cohort. Data from pregnancy registries have consistently shown, that the use of certain antiepileptic drugs (AEDs) during pregnancy increases the risk for specific congenital malformations. Petersen et al. determined that the prevalence of MCM ranges from 2.2%–6.6% [41]. All of the malformations described in our cohort have already been previously attributed to the use of AEDs [42]. The most common MCM associated with AEDs are neural tube defects, congenital heart disorders, urinary tract and skeletal abnormalities and cleft palate [3]. It's also known that in WWE who are taking AEDs, the risk of MCM to the fetus is dependent on the type, number and dose of AED [43–45]. The teratogenicity of valproate, in particular, has been well established [43,46]. However, in or study, those differences could not be verified due to the size of the sample. Polytherapy was associated with increased odds of MCM compared to monotherapy [6,47]. In fact, in almost all cases of malformations the mother was under polytherapy. We have a high compliance to folic acid supplementation in our study. Studies evaluating the effects of folic acid supplementation in pregnancy on major congenital malformation have shown positive results [42,48]. However, there is no current consistent standards specific to WWE about the recommendation for folic acid.

The strengths of this study include that our study database was prospectively recorded and details could be acquired by a comprehensive review of their medical records and by telephone interviews by neurologists; our analysis provided a large number of comparisons concerning obstetrical and neurological outcomes (most of studies just address few aspects of pregnant epileptic patients). Furthermore, we could perform a detailed monitoring of multiple potential confounding factors in our research and rigorous definitions of outcomes were applied [10]. This study has also some limitations that need to be acknowledged to better interpret the results. First, though the sample size was adequate for comparisons of the main outcomes, it was too small to perform specific subgroup analysis. Our study was not a population-based study, and therefore it is unclear to what extent findings can be generalized. In addition, as an observational study, some variables may be implicated in the outcomes of pregnancy and epilepsy. Another possible limitation is that no information was available on serum drug levels or the reasons for making treatment changes, which remain open to speculation. However, there is no consensus on when standardised drug concentration samples should be drawn or how they should be analysed to best reflect fetal exposure during the critical time window for teratogenesis [49]. Moreover, treatment decisions are complex, individualized and may change over time, what makes almost unfeasible to describe them in this type of study.

5. Conclusions

This study reflects the real experience of women with refractory epilepsy attending a tertiary neurology clinic in Brazil. A multicentre study reflecting wider practice in Brazil might achieve more significant data. Adequate engagement with women with epilepsy is needed during preconception and pregnancy to plan appropriate management. Poorly controlled patients with epilepsy may require active management during pregnancy by their neurologists working closely with obstetricians. Treatment and provision of care depends on quantification of the risks associated with pregnancy in women with refractory epilepsy. On the basis of our findings, women with refractory epilepsy should be informed that a significant risk of obstetric and neurological complications can occur. Patients with refractory epilepsy might have less odds of being seizure-free during pregnancy when compared to other types of epilepsy. Further studies concerning refractory epilepsy in pregnant women are encouraged.

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Conflicts of interest

The authors (Vitturi B.K., Cabral F.B. and Cukiert C.M.) do not have any conflicts of interest to disclose.

References

[1] Pennell PB. Pregnancy in women who have epilepsy. Neurol Clin 2004;22(4). https://doi.org/10.1016/j.ncl.2004.07.004.
[2] Harden CL, Hopp J, Ting TY, et al. Management issues for women with epilepsy-Focus on pregnancy (an evidence-based review): I. Obstetrical complications and change in seizure frequency. Epilepsia 2009;50(5):1229–36. https://doi.org/10.1111/j.1528-1167.2009.02128.x.
[3] Artama M, Auvinen A, Raudaskoski T, Isojärvi I, Isojärvi J. Antiepileptic drug use of women with epilepsy and congenital malformations in offspring. Neurology 2005;64(11):1874–8. https://doi.org/10.1212/01.WNL.0000163771.96962.1F.
[4] Chen YH, Chiou HY, Lin HC, Lin HL. Affect of seizures during gestation on pregnancy outcomes in women with epilepsy. Arch Neurol 2009;66(8):979–84. https://doi.org/10.1001/archneurol.2009.142.
[5] Sveberg L, Svalheim S, Taubøll E. The impact of seizures on pregnancy and delivery. Seizure 2015;28:35–8. https://doi.org/10.1016/j.seizure.2015.02.020.
[6] Tomson T, Perucca E, Battino D. Navigating toward fetal and maternal health: the challenge of treating epilepsy in pregnancy. Epilepsia 2004;45(10):1171–5. https://doi.org/10.1111/j.0013-9580.2004.15104.x.
[7] Vajda F, Bonizzoni E, Lindhout D, et al. Seizure control and treatment changes in pregnancy: observations from the EURAP epilepsy pregnancy registry. Epilepsia 2013;54(9):1621–7. https://doi.org/10.1111/epi.12302.
[8] Tomson T, Battino D, Bonizzoni E, et al. Seizure control and treatment in pregnancy: observations from the EURAP epilepsy pregnancy registry. Neurology 2006;66(3):354–60. https://doi.org/10.1212/01.wnl.0000195888.51845.80.
[9] Engel J. Approaches to refractory epilepsy. Ann Indian Acad Neurol 2014;17(Suppl 1):S12–7. https://doi.org/10.4103/0972-2327.128644.
[10] Tomson T, Battino D, Craig J, et al. Pregnancy registries: differences, similarities, and possible harmonization. Epilepsia 2010;51(5):909–15. https://doi.org/10.1111/j.1528-1167.2010.02525.x.
[11] Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2002;342(5):314–9. https://doi.org/10.1056/nejm200002033420503.
[12] Jones RM, Butler JA, Thomas VA, Peveler RC, Prevett M. Adherence to treatment in patients with epilepsy: associations with seizure control and illness beliefs. Seizure 2006;15(7):504–8. https://doi.org/10.1016/j.seizure.2006.06.003.

[13] Garber MC, Nau DP, Erickson SR, Aikens JE, Lawrence JB. The concordance of self-report with other measures of medication adherence: a summary of the literature. Med Care 2004;42(7):649–52. https://doi.org/10.1097/01.mlr.0000129496.05898.02.
[14] Harden C, Lu C. Epilepsy in pregnancy. Neurol Clin 2019;37(1):53–62. https://doi.org/10.1016/j.ncl.2018.09.008.
[15] Pennell PB. Pregnancy, epilepsy, and women's issues. Contin Lifelong Learn Neurol 2013;19(3):697–714. https://doi.org/10.1212/01.CON.0000431383.14061.e6.
[16] Kochen S. Pregnant women with epilepsy in a developing country. Open Neurol J 2011;5:63–7. https://doi.org/10.2174/1874205X01105010063.
[17] Shahla M, Hijran B, Sharif M. The course of epilepsy and seizure control in pregnant women. Acta Neurol Belg 2018;118(3):459–64. https://doi.org/10.1007/s13760-018-0974-0.
[18] Thomas SV, Syam U, Devi JS. Predictors of seizures during pregnancy in women with epilepsy. Epilepsia 2012;53(5):e85–8. https://doi.org/10.1111/j.1528-1167.2012.03439.x.
[19] Battino D, Tomson T, Bonizzoni E, et al. Seizure control and treatment changes in pregnancy: Observations from the EURAP epilepsy pregnancy registry. Epilepsia 2013;54(9):1621–7. https://doi.org/10.1111/epi.12302.
[20] Vajda FJE, O'Brien TJ, Graham JE, Hitchcock AA, Lander CM, Eadie MJ. Predicting epileptic seizure control during pregnancy. Epilepsy Behav 2018;78:91–5. https://doi.org/10.1016/j.yebeh.2017.10.017.
[21] Vajda FJE, O'Brien TJ, Lander CM, Graham J, Eadie MJ. Does pregnancy *per se* make epilepsy worse? Acta Neurol Scand 2015;133(5):380–3. https://doi.org/10.1111/ane.12479.
[22] Brodtkorb E, Reimers A. Seizure control and pharmacokinetics of antiepileptic drugs in pregnant women with epilepsy. Seizure 2008;17(2):160–5. https://doi.org/10.1016/j.seizure.2007.11.015.
[23] Vajda FJE, Hitchcock A, Graham J, O'Brien T, Lander C, Eadie M. Seizure control in antiepileptic drug-treated pregnancy. Epilepsia 2008;49(1):172–6. https://doi.org/10.1111/j.1528-1167.2007.01412.x.
[24] Reisinger TL, Newman M, Loring DW, Pennell PB, Meador KJ. Antiepileptic drug clearance and seizure frequency during pregnancy in women with epilepsy. Epilepsy Behav 2013;29(1):13–8. https://doi.org/10.1016/j.yebeh.2013.06.026.
[25] Otani K. Risk Factors for the Increased Seizure Frequency during Pregnancy and Puerperium. Psychiatry Clin Neurosci 1985;39(1):33–41. https://doi.org/10.1111/j.1440-1819.1985.tb01942.x.
[26] Patel SI, Pennell PB. Management of epilepsy during pregnancy: an update. Ther Adv Neurol Disord 2016;9(2):118–29. https://doi.org/10.1177/1756285615623934.
[27] Ernst L de L, Harden CL, Pennell PB, et al. Medication adherence in women with epilepsy who are planning pregnancy. Epilepsia 2016;57(12):2039–44. https://doi.org/10.1111/epi.13586.
[28] Ferrari CMM, De Sousa RMC, Castro LHM. Factors associated with treatment non-adherence in patients with epilepsy in Brazil. Seizure 2013;22(5):384–9. https://doi.org/10.1016/j.seizure.2013.02.006.
[29] Getnet A, Woldeyohannes SM, Bekana L, et al. Antiepileptic drug nonadherence and its predictors among people with epilepsy. Behav Neurol 2016. https://doi.org/10.1155/2016/3189108.
[30] Lu YT, Hsu CW, Tsai WC, et al. Status epilepticus associated with pregnancy: a cohort study. Epilepsy Behav 2016;59:92–7. https://doi.org/10.1016/j.yebeh.2016.03.034.
[31] Rajiv KR, Radhakrishnan A. Status epilepticus in pregnancy: etiology, management, and clinical outcomes. Epilepsy Behav 2017;76:114–9. https://doi.org/10.1016/j.yebeh.2017.07.002.
[32] Wu M, Hao N, Yan B, Chi X, Zhou D. Status epilepticus in pregnant women with epilepsy after valproate adjustment: a case series. Seizure 2016;43:39–41. https://doi.org/10.1016/j.seizure.2016.11.007.
[33] Borthen I, Eide MG, Daltveit AK, Gilhus NE. Obstetric outcome in women with epilepsy: a hospital-based, retrospective study. BJOG An Int J Obstet Gynaecol 2011;118(8):956–65. https://doi.org/10.1111/j.1471-0528.2011.03004.x.
[34] Ozdemir O, Sari ME, Kurt A, Sakar VS, Atalay CR. Pregnancy outcome of 149 pregnancies in women with epilepsy: experience from a tertiary care hospital. Interv Med Appl Sci 2015;7(3):108–13. https://doi.org/10.1556/1646.7.2015.3.4.
[35] Viale L, Allotey J, Cheong-See F, et al. Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis. Lancet 2015;386(10006):1845–52. https://doi.org/10.1016/S0140-6736(15)00045-8.
[36] Watila MM, Beida O, Kwari S, Nyandaiti NW, Nyandaiti YW. Seizure occurrence, pregnancy outcome among women with active convulsive epilepsy: one year prospective study. Seizure 2015;26:7–11. https://doi.org/10.1016/j.seizure.2015.01.007.
[37] Viinikainen K, Heinonen S, Eriksson K, Kälviäinen R. Community-based, prospective, controlled study of obstetric and neonatal outcome of 179 pregnancies in women with epilepsy. Epilepsia 2006;47(1):186–92. https://doi.org/10.1111/j.1528-1167.2006.00386.x.
[38] Walker SP, Permezel M, Berkovic SF. The management of epilepsy in pregnancy. BJOG An Int J Obstet Gynaecol 2009;116(6):758–67. https://doi.org/10.1111/j.1471-0528.2009.02141.x.
[39] Harden CL, Hopp J, Ting TY, et al. Practice parameter update: management issues for women with epilepsy - Focus on pregnancy (an evidence-based review): obstetrical complications and change in seizure frequency: report of the Quality Standards Subcommittee and Therapeutics and Technology A. Neurology 2009;73(2):126–32. https://doi.org/10.1212/WNL.0b013e3181a6b2f8.
[40] Alonso BD, da Silva FMB, RD de O Latorre Mdo, Diniz CSG, Bick D. Caesarean birth rates in public and privately funded hospitals: a cross-sectional study. Rev Saude Publica 2017;51:101. https://doi.org/10.11606/s1518-8787.2017051007054.
[41] Petersen I, Collings SL, McCrea RL, et al. Antiepileptic drugs prescribed in pregnancy and prevalence of major congenital malformations: comparative prevalence studies. Clin Epidemiol 2017;9:95–103. https://doi.org/10.2147/CLEP.S118336.
[42] Veiby G, Daltveit AK, Engelsen BA, Gilhus NE. Pregnancy, delivery, and outcome for the child in maternal epilepsy. Epilepsia 2009;50(9):2130–9. https://doi.org/10.1111/j.1528-1167.2009.02147.x.
[43] Tomson T, Battino D, Bonizzoni E, et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. Lancet Neurol 2011;10(7):609–17. https://doi.org/10.1016/S1474-4422(11)70107-7.
[44] Tomson T, Battino D, Bonizzoni E, et al. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. Lancet Neurol 2018;17(6):530–8. https://doi.org/10.1016/S1474-4422(18)30107-8.
[45] Tomson T, Battino D. Teratogenic effects of antiepileptic drugs. Lancet Neurol 2012;11(9):803–13. https://doi.org/10.1016/S1474-4422(12)70103-5.
[46] Hernández-Díaz S, Smith CR, Shen A, et al. Comparative safety of antiepileptic drugs during pregnancy. Neurology 2012;78(21):1692–9. https://doi.org/10.1212/WNL.0b013e3182574f39.
[47] Vajda FJE, Hitchcock A, Graham J, et al. Foetal malformations and seizure control: 52 Months data of the Australian Pregnancy Registry. Eur J Neurol 2006;13(6):645–54. https://doi.org/10.1111/j.1468-1331.2006.01359.x.
[48] Morrow JI, Hunt SJ, Russell AJ, et al. Folic acid use and major congenital malformations in offspring of women with epilepsy: a prospective study from the UK Epilepsy and pregnancy register. J Neurol Neurosurg Psychiatry 2009;80(5):506–11. https://doi.org/10.1136/jnnp.2008.156109.
[49] Voinescu PE, Park S, Chen LQ, et al. Antiepileptic drug clearances during pregnancy and clinical implications for women with epilepsy. Neurology 2018;91(13):e1228–36. https://doi.org/10.1212/WNL.0000000000006240.