Original Articles

Prevalence of epilepsy in Saudi pregnant women and possible effects of anti-epileptic drugs on pregnancy outcomes

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ABSTRACT

الأهداف : تحديد مدى انتشار الصرع في النساء الحوامل السعوديات وتقدير وتيرة النوبات في الحوامل الذين يستخدمون أنواع مختلفة من الأدوية المضادة للصرع . كما تهدف إلى الإبلاغ عن الآثار المسخية للأدوية المضادة للصرع كما لوحظ في حديثي الولادة.

المنهجية : أجريت هذه الدراسة المستقبلية في مستشفى الملك فهد الجامعي في الفترة من يونيو 2018 إلى يوليو 2019 . وأدرجت هذه الدراسة ثمانية وستون من النساء الحوامل المصابات بالصرع . تم تسجيل أنواع النوبات وترددداتها جنبًا إلى جنب مع الأدوية المضادة للصرع وعلاقتها بتشوهات الجنين / حديثي الولادة.

النتائج : من بين 68 أنثى مصابة بالصرع، حدثت 30 (44.1%) نوبة جزئية و 38 (55.9%) نوبة معممة . تسعة وثلاثون (57.3%) تلقوا علاجًا أحاديًا، و 21 (30.9%) تلقوا علاجًا متعددًا و 8 (11.8%) لم يتناولوا أدوية مضادة للصرع أثناء الحمل . لم يحدث لدى 36 (52.9%) من المرضى أي تغير في وتيرة النوبة أثناء الحمل، 19 (27.9%) شهدت زيادة في وتيرة النوبة و 13 (19.1%) أظهرت انخفاض وتيرة النوبة . متابعة نتائج الحمل أظهرت وفاة 2 (2.9%) جنين داخل الرحم، في حين ظهرت تشوهات في الوجه أو الأعضاء لدى 4 (4.9%) حديثي الولادة.

الخلاصة : تم العثور على زيادة في تواتر النوبات في 27.9% من الحوامل في العينة . كانت معدلات التشوه والوفيات أعلى في الأجنة / حديثي الولادة من المرضى الذين يعانون من نوبات معممة . وقد لوحظ أنه بالنسبة لمجموعة المرضى الذين يستخدمون العلاج الأحادي، كان معدل الأطفال الأصحاء أعلى من المجموعة التي تستخدم العلاج المتعدد.

Objectives: To determine the prevalence of epilepsy in Saudi pregnant women and estimate the frequency of seizure types in suffering individuals using different anti-epileptic drug modalities. It also aimed to report the teratogenic effects of anti-epileptic drugs as observed in neonates.

Methods: This prospective study was conducted at King Fahd University Hospital from June 2018 to July 2019. Sixty-eight pregnant women diagnosed with epilepsy were included in this study. Seizure types and their frequencies were recorded along with anti-epileptic drug therapies and their association with fetal/neonatal malformations.

Results: Out of 68 epileptic pregnant females, 30 (44.1%) experienced focal seizures and 38 (55.9%) experienced generalized seizures. Thirty-nine (57.3%) received monotherapy, 21 (30.9%) received polytherapy and 8 (11.8%) did not take antiepileptic drugs during pregnancy. Thirty-six (52.9%) patients experienced no change in seizure frequency during pregnancy, 19 (27.9%) experienced increase in seizure frequency and 13 (19.1%) showed decreased seizure frequency. The pregnancy outcomes analysis showed 2 (2.9%) intrauterine fetal deaths, whereas 4 (4.9%) neonates showed facial and/or organ malformations.

Conclusion: The frequency of seizures was found to increase in only 27.9% of the pregnant women in the sample. Malformation and mortality rates were higher in fetuses/neonates of patients with generalized seizures. It was observed that for the patient group using monotherapy, the rate of healthy babies was higher than that of the group using polytherapy.

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Epilepsy is defined as a brain disorder characterized by an enduring predisposition to generate epileptic seizures, with cognitive, neurobiological, psychological, and social consequences.[1] An epileptic seizure is "a transient occurrence of signs and symptoms due to abnormal excessive or synchronous neuronal activity in the brain".[1] According to the World Health Organization (WHO), it is the second most burdensome neurological disorder that can cause cognitive, neurobiological and psychosocial abnormalities in the suffering individuals.[2,3] In women with epilepsy (WWE), disruption of menstruation cycle, fertility, pregnancy, fetus development, menopause and sexual dysfunction has been reported.[4] The condition becomes more critical when WWE become pregnant. It has been estimated that the maternal death rate for this group is 10 times higher as compared to normal pregnancy cases.[5] Moreover, the frequent seizures during pregnancy have been known to jeopardize the cognitive and physical development of the fetus.[6] Thus, epilepsy is not only harmful for the mother but may also pose potentially worse consequences for the fetus.

The management of seizures through anti-epileptic drugs (AEDs) in pregnant WWE is a challenging task because during the risk-benefit assessment, the needs of the suffering WWE against the potential adverse effects of AEDs on the fetus need to be taken into account as well.[7] Several studies suggest the association of AEDs with congenital malformations which put physicians in a difficult spot. In this challenging situation, the attending physician is expected to choose between the available treatment options (mono- or polytherapy) during pregnancy. Therefore, the most critical issue is the regulation of the minimum effective dose of AEDs during pregnancy to prevent any damage to the fetus from seizures as well as AEDs.[8]

A plethora of evidence has reported the prevalence of epilepsy and its possible outcomes in the general population.[2,9,10] However, less is known about the prevalence of epilepsy in Saudi pregnant women, the association of AEDs with the frequency of seizures and their impact on fetal development. The quantification of epileptic pregnant patients and their pregnancy outcomes is important in order to provide optimal counseling and patient care. Therefore, the aims of this study were multifold: (1) to determine the prevalence of epilepsy in pregnant females, (2) to estimate the frequency of seizure types in suffering individuals using different anti-epileptic drug modalities, (3) to assess pregnancy outcomes and possible birth defects in WWE taking monotherapy, polytherapy or no therapy during pregnancy.

Methods. *Study Population.* This prospective study was conducted in a Tertiary Care Teaching and Referral Hospital, King Fahd University Hospital, Khobar, Saudi Arabia between June 2018 to July 2019. This hospital has the highest number of antenatal attendances in the eastern province for both normal and high-risk cases. Pregnant patients with active epilepsy admitted to the Obstetrics and Gynecology outpatient clinic and those seeking follow-up from our outpatient clinic were recruited in this study. Inclusion criteria was patients with active epilepsy and on treatment and those who had at least one seizure in the past one year.[3] Patients with single episode of seizure older than one year or seizure from a metabolic or other chronic disorder were excluded from the study. Misdiagnosed seizures such as syncopial attacks, and those who had past history of seizures due to eclampsia were also excluded.

Instrument. In this study, patients' information was collected through a structured questionnaire 'Questionnaire for Investigation of Epilepsy in Tropical Countries'[3] which was modified according to the study objectives. The following information was obtained from the history, physical and neurological examination of the patients and through QuadraMed® hospital database (ICD-9 coding system);

Seizure semiology according to the classification of the International League Against Epilepsy (ILAE)11; Type and duration of epilepsy; Type and dosage of anti-epileptic drugs; Electroencephalogram (EEG); Magnetic Resonance Imaging (MRI); Frequency of seizures during pregnancy; Fetal or neonatal weight, height, head circumference and presence of malformation.

Ethical considerations. The ethical approval was obtained from the institutional review board of Imam Abdulrahman Bin Faisal University after comprehensive review of the study protocols. The purpose of the study was explained to the patients in both oral and written form and informed consent was obtained. All items in the questionnaire were written in both English and Arabic for patients' convenience and clear understanding. For data collection, additional support was sought from the trainee students of the gynecology and obstetrics department.

Table 1 - Demographic and clinical characteristics of epileptic patients.

Variables	Monotherapy 39 (57.3)	Polytherapy 21 (30.9)	Without medication 8 (11.8)	*P*-value
	n (%)			
Average age ±SD (min-max)	28.79±5.8 (17–32)	31.2±6.3 (18–35)	23.6±2.1 (21–26)	0.12
Age of seizure onset	17.8±9.1 (1–35)	15.7±6.1 (3–32)	14.1±8.1 (2–29)	0.6
Disease duration (years)	12.6±8.9 (1–35)	7.3±5.6 (3–32)	9.2±9.1 (2–29)	0.7
Duration of use of AED (years)	11.7±9.07 (0.17–31)	12.3±7.3 (0.08–24)	1.8±2.02 (0–4)	0.1
Seizure semiology, n (%)				
Focal seizure	16 (41.0)	11 (52.4)	3 (37.5)	0.36
Generalized seizure	23 (59.0)	10 (47.6)	5 (62.5)	
Number of pregnancies, n (%)				
Nulliparous	27 (69.2)	14 (66.7)	6 (75.0)	0.34
Multiparous	12 (30.8)	7 (33.3)	2 (25.0)	
Electroencephalogram, n (%)				
Normal	15 (38.5)	5 (23.8)	5 (62.5)	0.6
Abnormal	24 (61.5)	16 (76.2)	3 (37.5)	
Cerebral imaging (MRI), n (%)				
Abnormal	7 (17.9)	6 (28.6)	0 (0)	0.5

Table 2 - Association between the frequency of seizures during pregnancy with neonatal birth weight, head circumference and height.

Parameters	Seizure frequency in pregnancy: unchanged / decreased / increased			P-value
	Unchanged	Decreased	Increased	
	Mean±SD Median (Min-Max)			
Birth weight (g)	3064±623 3105 (1360–4210)	3324±667 3410 (1200–4150)	3122±675 3110 (1910–3620)	0.812
Head circumference (cm)	33.127±2.469 34 (28–37)	34.965±1.990 34 (30–38)	32.767±2.369 33 (29–37)	0.832
Height (cm)	48.47±3.441 50 (40–53)	49.08±3.777 49 (41–51)	47.75±3.306 49 (40–52)	0.626

Statistical analysis. IBM SPSS Statistics package, Version 23.0 (IBM Corp, Armonk, NY, USA) was used for statistical analysis of the data. Numbers and percentages were used to represent categorical measurements, whereas, mean and standard deviation were used for numerical measurements. To compare categorical measurements between the groups, chi-square test was used and to compare the numerical measurements that did not show normal distribution between the 2 groups, Mann-Whitney U-test was used. For general comparison between more than two groups that did not show normal distribution, Kruskal-Wallis test was used. Statistical significance was taken as 0.05 in all tests.

Results. A total of 5872 patients were screened out of which 157 (2.67%) had either a past history of epileptic events or had an active epilepsy. From these 157 cases, 89 were excluded; 72 had a past history of seizure due to eclampsia, 13 had syncopial attacks misdiagnosed as epilepsy, and 4 had a single seizure episode older than one year. Among the 68 female patients included in the study, the mean age was 27.49±6.8 (min:17, max:35). It was observed that 39 (57.3%) of the patients included in the study received monotherapy, 21 (30.9%) received polytherapy treatment and 8 (11.8%) did not take antiepileptic drugs during pregnancy. Demographic and clinical information of the patients according to the treatment (monotherapy / polytherapy / non-medication) is shown in **Table 1**. There were 11 patients (16.2%) who used folic acid before pregnancy, 53 patients (77.9%) started folic acid after learning about pregnancy and 4 patients (5.9%) never used folic acid.

Table 3 - Clinical data of patients experiencing fetal/neonatal malformation or stillbirth.

Sr #	Seizure Semiology	Medication used	Frequency of seizures during pregnancy	Malformation Category	Malformation Name
Patient 1	Generalized seizure	CBZ 900 mg/day	Increased	Intrauterine death	Severe intrauterine growth restriction leading to intrauterine fetal death
Patient 2	Focal seizure	CBZ 1000 mg/day LMT 200 mg/day	Decreased	Facial malformation	Cleft lip and cleft palate
Patient 3	Generalized seizure	VPA 500 mg/day LMT 50 mg/day	Unchanged	Intrauterine death	Fetal anencephaly leading to still birth
Patient 4	Focal seizure	CBZ 400 mg/day	Unchanged	Organ malformation	Tetralogy of Fallot
Patient 5	Generalized seizure	VPA 1250 mg/day LMT 800 mg/day	Unchanged	Organ malformation	Atrial septal defect
Patient 6	Generalized seizure	No drug use	Unchanged	Facial + Organ malformation	Fetal gastroschisis along with cleft palate
CBZ - carbamazepine, VPA - valproic acid, LMT - lamotrigine					

The AEDs used were as follows; monotherapy users [n=39 (57.3%): lamotrigine (LMT)=20, levetiracetam (LEV)=9, carbamazepine (CBZ)=5, oxcarbazepine (OXC)=3, topiramate (TPM)=1, valproic acid (VPA)=1], polytherapy users [n=21 (30.9%); CBZ + LMT: 6, CBZ + LEV: 6, VPA + LMT: 3, VPA + CBZ: 3, LMT + LEV: 1, TPM + LEV: 1, LEV + OXC: 1, LMT + TPM: 1], n=8 (11.8%) did not use drugs.

Thirty (44.1%) of the patients had focal seizures and 38 (55.9%) had generalized seizures. There was no statistical difference in terms of the AED groups (polytherapy / monotherapy) used by patients with focal and generalized seizures (p=0.36). The EEG was normal in 25 (36.8%) and abnormal (focal slowdown, focal epileptic, secondary generalized epileptic activity) in 43 (63.2%) of the patients. Cerebral imaging (MRI) revealed focal lesions in 13 (19.1%) of the patients. MRI abnormalities included; thrombus in the cerebral vein, signal pathology in the frontal lobe, inactive demyelinating plaques, venous angioma in the frontal lobe, cystic astrocytoma in the temporal lobe, cerebellar atrophy, and/or sequelae of the left frontal tissue.

During pregnancy, 36 (52.9%) of the patients experienced no change in seizure frequency, 19 (27.9%) had increased seizure frequency, and 13 (19.1%) had decreased seizure frequency. The relationship between seizure frequency during pregnancy and neonatal birth weight, head circumference and height was found to be statistically insignificant (**Table 2**).

Out of the 68 WWE, malformation or still birth was observed in 6 (8.8%) of the fetuses/neonates. Out of these 6 cases, 2 had intrauterine death, whereas, malformation (facial, organ or both) was seen in the remaining 4 neonates. The clinical data of these 6 patients experiencing fetal/neonatal abnormalities is given in **Table 3** along with their AED regime and its effect on seizure frequency. These abnormalities included; cleft lip and palate, tetralogy of Fallot, atrial septal defect and fetal gastroschisis (**Table 3**).

Discussion. Many regional studies have reported the perceptions and attitude of the general population towards epilepsy[10,12] and its prevalence which is known to be roughly 6.54 among every 1000 Saudi individuals.[13] The results revealed the prevalence to be 2.67%, which is significantly lower than some studies[14] but higher than the others.[3,15] In general, the literature indicates a higher prevalence of epilepsy in under-developed countries as compared to this study.

This lower prevalence rate could be due to differences in study designs in studies of a similar nature. Another probable cause of this result could be that this study was conducted in a tertiary care hospital. It is well known that community-based studies usually report a higher prevalence as compared to hospital-based studies.[16] Moreover, women with no or less formal education mostly have a poor health-seeking attitude which could also explain the lower prevalence.[17] Another very important factor that could be responsible for the lower prevalence found in this study is the social stigma associated with this disorder.[16]

Furthermore, the occurrence of generalized seizure (55.9%) was observed to be more than that of focal seizure (44.1%), which is consistent with the findings of other local studies.[13,18] More than half of the pregnant WWE described no change in seizure frequency during pregnancy, which is consistent with the findings of the European and International Registry of Antiepileptic Drugs and Pregnancy.[19] Conversely, Patel and Pennell[20] reported an increase

in seizure frequency among one-third of their patient population of pregnant women. Unfortunately, there is no local study to compare the results. Additionally, no statistically significant association was observed between the change in seizure frequency and neonatal birth parameters. This could be attributed to the small sample size; otherwise, studies suggest that neonates born to AED taking WWE are usually at higher risk for postnatal complications, such as microcephaly and low birth weight among other issues.[20]

The goal in the clinical management of epileptic pregnant patients is to reduce seizures with minimal fetal exposure to AEDs. This is often challenging for the attending physician because AEDs are known for their teratogenic effects causing major congenital malformations, deficits in neurocognitive development intrauterine growth retardation and still births.[5,20,21] In the current study, major congenital malformations were observed in 6 patients. Two intrauterine deaths were observed in patients suffering from generalized seizures. The rate of stillbirth and congenital malformations in the present study was higher in patients receiving polytherapy as compared to patients receiving monotherapy. A similar trend was observed by Battino and colleagues,[19] who found more congenital malformations in neonates born to patients on multiple AEDs. Though many works suggest increased likelihood of malformations in polytherapy cases, the association of these malformations to genetic and environmental factors should not be overlooked.

The present study also contained some limitations. First, as it was a hospital-based study, it can be considered that the observed prevalence may not be a true reflection of the whole community. Furthermore, it is highly likely that some women might have not disclosed their epileptic status due to social fear and stigmatization. Thus, it may be difficult to generalize the findings of this study. Second, the sample size of the study was small which may have affected the statistical power of the analysis. Lastly, the serum concentration of AEDs was not measured to explore patient compliance with medication and reliance was placed on verbal information which may not be a completely reliable source.

In conclusion, A 2.67% prevalence of active epilepsy among pregnant women was observed, with higher occurrence rate of generalized seizures as compared to focal onset. It was found that more than 50% of the pregnant patients diagnosed with epilepsy did not experience a change in the frequency of seizures during the period of regular drug use. Malformation and mortality rates were higher in fetuses/neonates of patients with generalized seizures. It was observed that the rate of healthy babies for the patient group receiving monotherapy was higher than that compared to the group on polytherapy. The findings of this study may generate research interest in further exploring the pregnancy outcomes of WWE on different AED regimes in our region. Studies of this kind will help physicians to better optimize AEDs and control seizures during pregnancy, thus enhance overall pregnancy outcomes in epileptic women. More reliable results can be achieved by conducting similar but longitudinal studies at multiple centers with a larger sample size.

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Statistics

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