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Seizure occurrence, pregnancy outcome among women with active convulsive epilepsy: One year prospective study

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ABSTRACT

Purpose: To determine the prevalence of active convulsive epilepsy, seizure frequency and the outcome of pregnancy amongst a cohort of pregnant women attending antenatal clinic (ANC) at two tertiary hospitals.

Methods: An observational cohort study conducted at the University of Maiduguri Teaching Hospital and State Specialist Hospital, Northeast Nigeria. Pregnant women attending antenatal care were screened for previous history of active convulsive epilepsy, and recruited consecutively according to a specified protocol. A standardized questionnaire was administered to record pregnancy history, nature of epilepsy and treatments received. They were followed-up during the course of the pregnancy based on the ANC schedule up to delivery. The outcome of pregnancies was recorded.

Results: A total of 7063 pregnant women were screened, of whom 103 (1.46%) subjects had at least a past history of seizure. Seventy-eight (1.10%) had a past history of seizure(s) from eclampsia and 23 (0.33%) pregnant subjects recruited were identified to have active convulsive epilepsy. The unadjusted prevalence of active convulsive epilepsy in pregnant women was found to be 3.33 per 1000 (95% CI: 2.1–4.8). Subjects who had a history of head injury and encephalitis were more likely to have seizures during pregnancy. ($P = 0.013$ and $P = 0.041$). Those who had recurrent seizures within the last six months before recruitment were more likely to have a negative pregnancy outcome ($P = 0.043$).

Conclusion: Our study found a prevalence of active epilepsy of 3.33 per 1000 among pregnant women, with about one percent having a past history of seizure from eclampsia.

1. Introduction

Epilepsy is a common and serious neurological condition characterized by an enduring predisposition to generate epileptic seizures with neurobiologic, cognitive, and psychosocial consequences [1,2]. The annual incidence of epilepsy in the developed countries is about 50–70 cases per 100,000 population and a prevalence of about 5–10 per 1000. The developing world accounts for a large percentage of cases with an incidence of 100–190 cases per 100,000 per year [3]. The lifetime prevalence of epilepsy may be lower in low- to middle-income countries (Laics), which is speculated to be due mainly to higher premature mortality [4]. A Nigeria study gave a crude prevalence of epilepsy at 533 per 100,000 [5]. Head trauma, cerebral infections and primitive obstetric services common in developing countries add to the burden of epilepsy [6–8].

Although the prevalence of epilepsy is slightly higher in men than in women [9,10]. Women with epilepsy (WWE) have been shown to have peculiar issues regarding management [11]. The burden of epilepsy is not well defined in women in LMICs [4], considering that a large proportion of them are within the childbearing age [12]. This is different in high income countries (HIC) where there is a growing concern for WWE with regards to marriage, fertility, pregnancy, childbirth, teratogenicity, menopause, and contraception [13–17]. Despite the treatment gap in epilepsy in LMIC [18]; WWE are by far more neglected in sub-Saharan Africa [19], with more likelihood of psychosocial distress compared to other chronic health conditions [11,19]. Some of the

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peculiar issues faced by WWE in sub-Saharan Africa include stigmatization, poor education, traditional and animistic beliefs, and fear of teratogenic effect of antiepileptic drugs (AEDs) in pregnancy [20–23]. These psychosocial issues often neglected are very important that most women fail to disclose their epileptic status, are inadequately managed and unwilling to take their medications [21]. Pregnancy, childbirth and puerperium is a period that requires proper management and seizure control; on the other hand, even the inappropriate use of AEDs may have deleterious effect on the mother and foetus [24,25].

Studies on pregnant WWE are lacking in North-east Nigeria. The prevalence and outcome of epilepsy among pregnant women have not previously been studied in our environment. There is also no proper ascertainment, counselling, and treatment for pregnant WWE in most hospitals in this region. Therefore we performed a study to determine the prevalence of pregnant WWE, follow them up over the course of their pregnancy; to determine the frequency of seizure and how this affects outcome of pregnancy in women attending antenatal clinics (ANCs) of two tertiary hospitals. This one year prospective study will provide preliminary data and serve as a pilot study for further multi-centre study that will provide large information on pregnant epileptics and foetal outcome in sub-Saharan Africa.

2. Materials and methods

2.1. Study population

This was a one year observational cohort study conducted at two ANCs of University of Maiduguri Teaching Hospital (UMTH) and the State Specialist Hospital (SSH) Maiduguri, Borno state, North east Nigeria, between September 2012 and August 2013. These two hospitals have the largest number of antenatal care attendance in the state both for normal antenatal care and referred cases. Subjects were consecutively recruited within an 8 month period (September 2012–April 2013) as they attended ANC for antenatal booking. In the recruitment process all women with viable pregnancy underwent a 3 stage screening. The first stage of screening was to determine those who have had any previous history of paroxysmal event(s) that may be suggestive of a seizure. Secondly, subjects who have had a history of any paroxysmal event in their lifetime were further screened to determine those who have had at least a seizure. The third stage is to determine those with epilepsy as defined by the International League Against Epilepsy (ILAE) as those who had 2 or more unprovoked seizure [26]. Subjects with active epilepsy (defined as those on treatment or those who had at least a seizure within the last one year) [27], were then recruited for the study. Most cases were ascertained from history, and are more likely to have active 'convulsive' epilepsy. For most subjects, consultations were made to a family member or friend who had witnessed the seizure episodes or their past medical records to ascertain the nature of such paroxysmal event(s). Those excluded from the study include; those with single episode of seizure, seizure from a metabolic or a reversible cause, misdiagnosed seizures as sync opal attacks, and women who have had seizures from eclampsia either from a previous or index pregnancy.

2.2. Instrument

We developed a standardized structured questionnaire, adapted and modified from 'Questionnaire for Investigation of Epilepsy in Tropical Countries', which was developed through collaborative work involving the Institute of Neurological Epidemiology and Tropical Neurology of Limoges France, the Pan-African Association of Neurological Sciences and the ILAE, for the purpose of standardizing epilepsy study in tropical countries [28]. Medical officers and midwives were trained on how to fill the questionnaire, perform basic examinations and follow-up the subjects. The questionnaire consists of questions to elicit socio-demographic characteristics (such as age, place of residence, educational attainment, ethnic group, employment and trade), relevant information on the index pregnancy, natural history of the seizure disorder, clinical classification of the seizure type based on ILAE classification, diagnosis of seizures and epileptic syndromes, predisposition, risk factors, and precipitating factors of epilepsy [26]. Both centres had experienced clinicians who were involved in case ascertainment, supervision of the filling of questionnaires, and assist in clinical diagnosis and classification of epilepsy [Questionnaire included as Supplement 1].

2.3. Treatment of pregnant epileptics

All treatments and doses received were documented. For subjects not on AEDs, consent is sought to commence appropriate medications if required. Common AEDs available in our hospital are: Phenytoin, Carbamezepine, Diazepam, Phenobarbital, Primidone, and Valproic acid. The commonest prescribed in women of child bearing age is Carbamezepine. Additionally, they are routinely prescribed haematinics containing iron and folic acid.

2.4. Follow-ups and delivery

The subjects were followed-up during the course of the pregnancy based on the ANC schedule. The conventional ANC schedule in these hospitals starts with ANC booking at the end of the first trimester. They are seen every 4 weeks until 28 weeks of gestation, then every 2 weeks until 36 weeks and weekly until delivery. The frequency and seizure types, including treatments were recorded during these visits, in addition to their routine antenatal consultations.

Delivery was conducted by an obstetrician registrar or a midwife at the labour wards of the hospitals. The method of delivery is documented. On delivery the newborn were examined; the APGAR score was calculated, and gestational age was determined. Adverse outcomes of pregnancy include; Stillbirth, foetal loss and congenital malformations. Those who had an uneventful pregnancy, delivery, and no adverse foetal outcome were considered to have a positive pregnancy outcome. All these information were recorded in the questionnaire.

The subjects were encouraged to come for follow-ups and to deliver in the designated hospitals. Telephone numbers, proper addresses of the patient were recorded for the ease of tracking them, since it is known that women in general and WWE may just prefer to deliver at home under the supervision of a traditional birth attendant [18,23].

2.5. Ethical methods

The study protocol was reviewed and approved by the Ethics Committee of the University of Maiduguri Teaching Hospital and the Borno State Ministry of Health. Informed consent was obtained before a candidate is enrolled in the study. All questionnaires written in English were interpreted into the common local languages, Hausa and Kanuri. Trained medical personnel were assigned to each of the designated clinics, who administered the Informed consent and the questionnaire.

2.6. Statistical analysis

Descriptive statistics was used to analyze characteristics. A univariate analysis was carried out using Fisher's Exact test for

categorical variables. Spearman's correlation was used to assess the relationship between the number of seizures during pregnancy and pregnancy outcome. A *P*-value of ≤0.05 was considered statistically significant. All analyses were done using the Statistical Package for Social Sciences. SPSS Version 16.0 SPSS Inc; Chicago, IL, USA.

3. Results

We screened a total of 7063 subjects, 5449 (77.1%) from the SSH and 1614 (22.9%) from the UMTH. The screening process and recruitment is summarized in Fig. 1. One hundred and eleven subjects (1.57%) had a past history of paroxysmal event. Those who have had at least a seizure in their lifetime irrespective of cause were 103 (1.46%). From which 88 (1.25%) subjects were excluded from the study; of those excluded 8 (0.11%) were diagnosed as syncopal attacks, 2 (0.03%) had previous single seizure episode more than five years ago and 78 (1.10%) had a past history of seizure from eclampsia. We identified 23 (0.33%) pregnant subjects with active convulsive epilepsy, who participated in the study. The unadjusted prevalence of epilepsy in pregnant women was found to be 3.33 per 1000 (95% CI: 2.1–4.8). Mean age of study participants was 23.7 ± 6.0 [Median 23.0 years; range 16–40 years].

The socio-demographic characteristics and seizure outcome, between those who had seizure during pregnancy and those who did not are shown in Table 1. There was no significant difference in the sociodemographic characteristic like; age groups, employment, education, living area and ethnicity, between these two groups. Subjects who had a past history of head injury and encephalitis were more likely to have seizures during pregnancy. ($P = 0.013$ and $P = 0.041$) There was no difference with use of AED in treatment between the two groups.

Seizure characteristic and pregnancy outcome in those with positive or negative pregnancy outcome is shown the Table 2. Those who had seizures within the last six months before recruitment were more likely to have a negative pregnancy outcome ($P = 0.043$). There were five subjects with negative outcome of pregnancy which includes one spontaneous abortion, one still birth, one intra-uterine foetal death, one neonatal sepsis & one congenital malformation (hypo plastic nail). No difference exists between the two groups regarding age of first seizure, seizure type, precipitants and treatment of epilepsy.

Table 3 depicts the use of AED and pregnancy outcome, showing no significant difference in outcome between the various AED types. It also shows no difference between drug compliance and pregnancy outcomes.

The relationship between seizure during pregnancy and pregnancy outcome is shown in Table 4. This observation although important, was not statistically significant.

The spearman's correlation shows that an inverse correlation (not statistically significant; $r = -0.089$; $P = 0.735$) exists between number of seizures during pregnancy and pregnancy outcome, as the number of seizures increase during pregnancy, pregnancy outcome tends towards a negative outcome.

Table 1
Socio-demographic characteristics and seizure outcome.

Variables	Seizures		Chi square	*P*-value
N = 23	Yes[a] *n* (%)	No *n* (%)		
Age group				
15–24years	2 (33.3)	12 (70.6)	5.218	.074
25–34years	4 (66.7)	3 (17.6)		
35–44years	0 (0)	2 (11.8)		
Employment				
Employed	3 (50.0)	2 (11.8)	3.811	.051
Unemployed	3 (50.0)	15 (88.2)		
Education				
Less than primary education	6 (100)	15 (93.8)	.393	.531
Primary education and more	0 (0.0)	1 (6.2)		
Living area				
Urban	4 (66.7)	13 (76.5)	.221	.638
Semi-Urban	2 (33.3)	4 (23.5)		
Ethnic groups				
Kanuri	2 (33.3)	11 (64.7)	1.776	.183
Others	4 (66.7)	6 (35.3)		
Family history of epilepsy				
Yes	1 (16.7)	3 (17.6)	.003	.957
No	5 (83.3)	14 (82.4)		
Head injury				
Yes	2 (33.3)	0 (0.0)	6.206	.013[b]
No	4 (66.7)	17 (100)		
Measles				
Yes	1 (16.7)	4 (23.5)	.123	.726
No	5 (83.3)	13 (76.5)		
Encephalopathy/encephalitis				
Yes	2 (33.3)	0 (0)	6.404	.041[b]
No	4 (66.7)	17 (100)		
Meningitis				
Yes	0 (0)	1 (5.9)	.369	.544
No	6 (100)	16 (94.1)		
Treatment with AED				
Yes	1 (16.7)	7 (41.2)	1.174	.278
No	5 (83.3)	10 (58.8)		

[a] Seizures occurred during pregnancy.
[b] Statistically significance when $p < 0.05$.

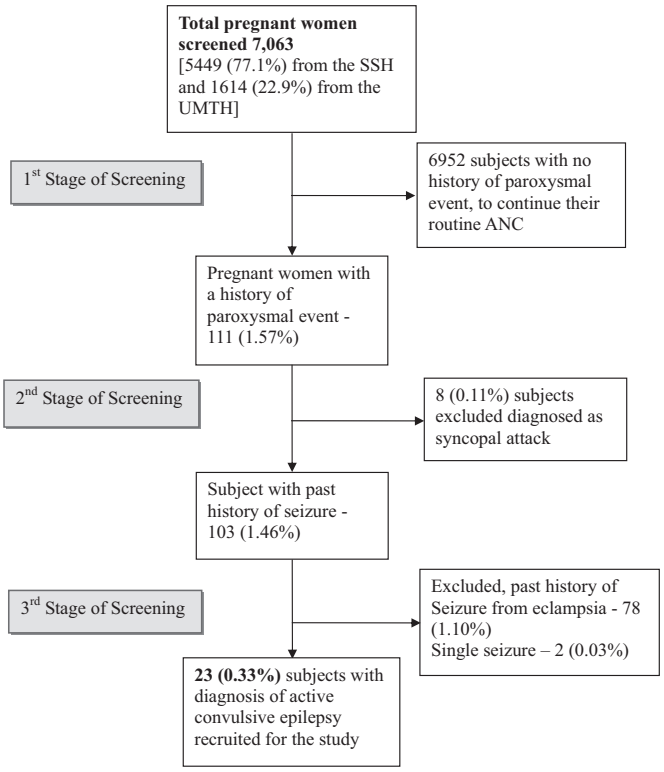

Fig. 1. Screening process and recruitment.

4. Discussions

This is the first prospective study that examined pregnant epileptics in Northeast Nigeria. Our study found a prevalence of active epilepsy of 3.33 per 1000 among pregnant women. The prevalence found in this study is lower than some studies [29,30], but higher than the study by Artama et al. [31]. Generally epilepsy studies reported a higher prevalence in developing countries than what was reported in this study [5,9,32]. The reason for a lower

Table 2
Seizure characteristics and pregnancy outcome.

Variables	Pregnancy outcome		Chi square	*P*-value
N = 23	Positive *n* (%)	Negative[a] *n* (%)		
Age at first seizure				
≤12years	5 (27.8)	1 (20.0)	.123	.726
>12years	13 (72.2)	4 (80.0)		
Last seizure occurrence				
< 6months	9 (50.0)	5 (100)	4.107	.043[c]
≥6months	9 (50.0)	0 (0)		
Seizure type				
Generalized seizure	14 (77.8)	5 (100)	1.345	.246
Partial seizure	4 (22.2)	0 (0)		
Precipitants of seizure[b]				
Emotion	7 (38.9)	4 (80.0)	2.65	.104
Alcohol	1 (5.6)	0 (0.0)	.290	.590
Sleep	3 (16.7)	0 (0.0	.958	.328
Lack of sleep	11 (61.1)	2 (40.0)	.710	.400
Flashing light	4 (22.2)	0 (0)	1.345	.246
Hyperventilation	2 (11.1)	1 (20)	.273	.602
Menstruation	7 (38.9)	0 (0.0)	2.795	.095
Treatment of epilepsy				
Traditional medication	7 (38.9)	1 (20.0)	.713	.870
AED	6 (33.3)	2 (40.0)		
AED & traditional medication	2 (11.1)	1 (20.0)		
None	3 (16.7)	1 (20.0)		

[a] Negative outcome of pregnancy includes spontaneous abortion, still birth, intra-uterine foetal death, neonatal sepsis & congenital malformation.
[b] Multiple response.
[c] Statistically significance when $P < 0.05$.

prevalence in this study may be due to differences in methodology. Our study was hospital-based and included only pregnant WWE. Community based studies generally report a higher prevalence [33]. Women have a poor health-seeking habits in sub-Saharan Africa which may also explain the lower prevalence [34]. Most of our women in this study were unemployed and without formal education, they are more likely to have limited information and seek access to health care. Other reasons for the lower prevalence in this study may be issues of stigmatizations [21,22], low fertility rate [35,36], and decrease sexual interest [37]. Increase mortality, especially in people with active convulsive epilepsy may also contribute to the lower prevalence [38]. These could be areas for further studies in our community.

During our screening we observed a high prevalence of eclampsia. It is a common cause of acute symptomatic seizures in women of reproductive age in sub-Saharan Africa; but generally not regarded as an epileptic disorder [39,40]. Further studies need to be conducted to determine whether it has any link or remote relationship with subsequent long term development of epilepsy.

Table 3
Use of AED and pregnancy outcome.

Variables	Pregnancy outcome		Chi square	*P*-value
N = 23	Positive *n* (%)	Negative *n* (%)		
AED type[a]				
Barbiturate	1 (5.6)	1 (20.0)	1.028	.311
Diazepam	0 (0)	2 (40.0)	7.886	.056
Carbamazepine	5 (27.8)	3 (60.0)	1.791	.181
Phenytoin	1 (5.6)	0 (0.0)	.290	.590
Valporic Acid	3 (16.7)	0 (0.0)	.958	.328
AED taken regularly				
Yes	6 (33.3)	2 (40.0)	.077	.782
No	12 (66.7)	3 (60.0)		

[a] multiple response.

Table 4
Relationship between seizure during pregnancy and pregnancy outcome.

Variables	Pregnancy outcome		Chi square	*P*-value
N = 23	Positive *n* (%)	Negative *n* (%)		
Seizure outcome				
No seizures	13 (72.2)	4 (80.0)	.123	.726
Had seizure	5 (27.8)	1 (20.0)		

Our study showed that those with a history of head injury and encephalitis were more likely to have persistent seizures in pregnancy; these aetiologies are commonly associated with seizure and epilepsy in Africa [7,41].

Those who had seizures within the last six months before recruitment in this study were more likely to have a negative pregnancy outcome; however we found no association between seizure occurrence during pregnancy and pregnancy outcome. This may suggest a relationship between long-term seizure control on pregnancy outcome due to recurrent and cumulative effect of recurrent seizure over a long time [42]. Our study found a non-significant inverse correlation between number of seizures during pregnancy and pregnancy outcome; the small sample size might explain the non-significance. A larger study involving more pregnant women with ACE is therefore warranted. A study by Chen et al. [43] observed that epileptic seizures during pregnancy were independently associated with increased risk of negative pregnancy outcome, suggesting that uncontrolled seizure during pregnancy and delivery may be associated with poor pregnancy outcome. The adverse effects of seizures on pregnancy outcome have been reported to be due to intrauterine haemorrhages, early abortion and still births; attributable to uterine injury and placental bruising or detachment [42]. The strength of the study is that, it is the first in this part of the country to examine epilepsy in a population of pregnant women. We also screened a large number of pregnant women. This study will form a template for further multicentre study. We observed from these ANCs that history of epilepsy is not asked routinely as done for other medical conditions like diabetes, hypertension and asthma.

There are several limitations in this study. Firstly, the small sample size and the short duration of the study will affect the statistical power of the study. This lack of power will make statistical inferences difficult and therefore giving more weight to statistical significance will be fraught with error. Secondly, it is a hospital-based study. The prevalence in this study may not be the true reflection of what obtains in the community, some women may not want to disclose their epileptic status due to issues of stigmatisations and fear that if others know about their diagnosis they may influence their husbands to abandon them [21,22]. Thirdly, being a resource poor setting, MRI scans and EEG were not available and therefore clinical characterization and classification of epilepsy could not be ascertained; this would have been useful as this study shows a bias for reporting generalized convulsive seizure compared to partial seizures. Fourthly, we did not include non-convulsive epilepsies, as this is difficult to ascertain in our environment. Fifthly, our lack of consideration of serum concentration of AEDs to help give an idea on those who are compliant to medications as most times verbal communication may not be relied on.

These methodological limitations does not invalidate the results as the gold standard for case ascertainment in epilepsy is still from clinical history elicited by an experienced clinician [26].

5. Conclusion

Our study found a prevalence of active epilepsy of 3.33 per 1000 among pregnant women, with about one percent having a past history of seizure from eclampsia. Despite the small sample size;

subjects who had a past history of head trauma and encephalitis were more likely to have seizure during pregnancy. Those with poor seizure control were more likely to have a negative pregnancy outcome. This study should generate interest in pregnant WWE in our region. We suggest that better optimization of AEDs and control of seizure before and during pregnancy will likely improve outcomes in pregnant epileptics.

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Conflict of interest

We declare that we have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2015.01.007.

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