ORIGINAL ARTICLE

Maternal and Foetal Outcome of Anti-epileptic Drug Use in Pregnancy in Afro-Caribbean Patients

S Rowe-Gardener[1,2], F Gayle[1,2], N Johnson[3]

ABSTRACT

Objective: *To determine the maternal and foetal outcomes of anti-epileptic drugs (AEDs) use during pregnancy, in women of Afro-Caribbean descent, seen at the University Hospital of the West Indies (UHWI).*

Methods: *A retrospective observational study was conducted for the period of 2002-12. From the records received, 40 cases were identified from the labour ward admission books and the Codes and Ethics Department. The controls were sought from the labour ward records and were matched for year of delivery, age ± 6 years and co-morbidities.*

Results: *An adverse foetal outcome was higher in infants exposed to AEDs in utero and was found to be statistically significant (*p *= 0.04). The occurrence of minor malformations in infants exposed to AED was determined to be more than two-times (14.2%) compared to the occurrence in infants from the control group (6.1%). The maternal outcomes from an exposure to AED in pregnancy were not found to be significantly different between cases and controls. (*p *= 0.06).*

Conclusion: *There are additional adverse effects of AED use in pregnancy, other than major congenital malformations (MCMs), such as an increased risk of foetal demise. Similar to the previous reports, there are adverse maternal outcomes of AED use, though the differences did not achieve conventional levels of statistical significance in this study.*

Keywords: Anti-epileptic drugs (AEDs), Afro-Caribbean, major congenital malformations (MCMs), maternal outcomes

INTRODUCTION

Epilepsy is the most common serious chronic neurological condition, affecting between 4 and 10 people per 1000 (1). Most of those affected, including women of childbearing age, will require a long-term treatment with anti-epileptic drugs (AEDs) to prevent seizures (1). It is widely accepted that the prenatal exposure to AEDs increases the risk of a major congenital malformation (MCM) from the background risk of 1%–2% to 4%–9% (1). However, the medical literature does note that more than 90% of pregnancies will be free of MCMs (1). There are other effects of AEDs such as respiratory distress (2), foetal demise (3) and neurodevelopmental effects that have been identified by following the infant from 2 years to several years after the birth (3–12). It is recommended that women who have to use AEDs take the smallest effective dose and/or utilize monotherapy as much as is possible (13, 14).

The mechanisms for the teratogenicity of AEDs are most likely multifactorial and may include genetic susceptibility, free radical intermediates of AEDs, enzymatic deficiencies causing accumulation of toxic intermediates of medications and AED-induced folate deficiencies (15). Despite the lack of irrefutable evidence, the American Academy of Neurology recommends that every woman with epilepsy of childbearing age receives

From: [1]Department of Medicine, Faculty of Medical Sciences, University of the West Indies, Kingston 7, Jamaica, [2]Department of Medicine, Faculty of Medical Sciences, University Hospital of the West Indies, Kingston 7, Jamaica, and [3]Department of Obstetrics and Gynecology, University of the West Indies, Kingston 7, Jamaica.

Correspondence: Dr S Rowe-Gardener, Department of Medicine, Faculty of Medical Sciences, University Hospital of the West Indies, Mona, Kingston 7, Jamaica. Email: drswane.gardener@gmail.com

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folate supplementation of at least 0.4 mg/day for primary prevention of neural tube defects and 5 mg/day for secondary prevention (13, 15, 16). Furthermore, women with epilepsy have an approximately twofold increased risk of certain obstetrical complications including hyperemesis gravidarum and abruptio placentae (17). It is uncertain as to whether or not these adverse effects are due to epilepsy or the use of AEDs in pregnancy.

The development of international pregnancy registers has generated useful information towards a greater understanding of the impact of AED exposure on immediate birth outcomes (18). Nevertheless, there were no data found looking at the difference in adverse effects among the different ethnic groups in either mother or child. This study aims to identify the adverse effects of AED/s use in pregnancy on mother and foetus in an Afro-Caribbean population. The statistical method used is the ANOVA analysis to determine the correlation between the AED use and the adverse effects identified. It is hoped that this study will encourage Jamaica and other Caribbean countries to consider starting a registry of pregnant women on AEDs. The results from such a registry could help many local neurologists and obstetricians to treat pregnant women, who require AEDs, with more confidence.

SUBJECTS AND METHODS

Study design

This is a retrospective observational case–control study conducted at the University Hospital of the West Indies (UHWI). The UHWI is a tertiary academic referral hospital with over 400 beds serving the capital city and its surrounding areas in Jamaica.

The cases were chosen based on the following inclusion criteria: All pregnant women who had epilepsy and were using AEDs or had epilepsy but were not using AEDs or those who do not have epilepsy but were using AEDs for conditions other than epilepsy, and were seen at the antenatal clinic (ANC) or admitted at the UHWI between 2002 and 2012. For each of the enrolled women, one woman was chosen who does not have epilepsy and is not taking AEDs. These controls were within a ± 6-year age range and were delivered the same year as the enrolled case. They were also matched for co-morbidities.

Patients were excluded if they: were not known to have epilepsy but had one seizure episode in the past and were not using AEDs; were not known to have epilepsy and not on AED but had eclampsia; had congenital malformations or family history of congenital malformations; had multiple gestations, alcoholic consumption or smoking during pregnancy; had acute infections during pregnancy.

Data collection

Forty index cases were identified from the labour ward admission books between 2002 and 2012. The cases were identified from a search of the labour ward admission books and the Codes and Ethics Department based on the code for pregnancy and epilepsy, migraine, bipolar disorder and neuropathic pain. The controls for each index case were sought from the labour ward records in the same year of delivery as the index case and were also matched for comorbid diseases. These controls did not have epilepsy and were not taking AEDs. Once the dockets were obtained, the pre-natal and post-natal notes up to six weeks following delivery were reviewed.

The maternal and foetal outcomes of the controls were then compared to the index cases. The study was approved by the University Hospital of the West Indies/University of the West Indies/Faculty of Medical Sciences Ethics Committee. Data were entered into a Microsoft Access database (see Appendix A) and included: medication regime, *i.e.*, single or polytherapy; time instituted prior to or during pregnancy. Polytherapy is defined as taking two or more AEDs concurrently regardless of the time, the subsequent drug was added. The maternal and foetal outcomes observed for were similar to the outcomes found in the previous studies to be associated with AED/s use in pregnancy.

RESULTS

Of the forty records reviewed, seven cases were rejected and omitted from the final analysis due to the inadequate antenatal records or unavailable dockets. The final review was conducted on 33 index cases and 33 controls. The categories of women analysed in this study are shown in Table 1. Most (63%) women who used AED used monotherapy and 55% used multiple drugs including the combination therapy throughout pregnancy.

A total of 27 women were identified who had taken one or more anti-convulsant drugs during pregnancy, 17 of whom took only one drug and 10 of whom had taken two or more drugs. Carbamazepine was the most commonly used drug, used by 14 women, followed by valproic acid, used by 13 women, phenytoin by 9 women, phenobarbital by 2 women and diazepam by 2 women. Three women used newer types of AEDs, one woman used lamotrigine and two used topiramate. Among the 27

Table 1: Types of seizures occurring during pregnancy and AED use

Category	Women used AED		Women did not use AED		Total
	Seizure	No seizure	Seizure	No seizure	
Identified cases	21	6	6	33	66
Seizure Dev[1] in pregnancy	1	0	0	0	1
Seizure during pregnancy	9	0	0	0	9
Partial seizure	3	0	0	0	3
Generalized tonic clonic seizure	5	0	0	0	5
Not indicated	1	0	0	0	1
AED drug use					
Mother took only 1 AED	11	6			17
Mother took only 2 AED	6	0			6
Mother took only 3 AED	3	0			3
Mother took only 4 AED	1	0			1
Mother took AED in comb[2]	5	0			5

[1] Refers to seizures developed in pregnancy.
[2] Refers to women who used more than one AEDs in combination.
AED = anti-epileptic drug.

women who used at least one anti-convulsant drug, six used the drug for migraine. Of that number, four (66.7%) used valproic acid and two (33.3%) used topiramate.

The foetal outcomes in each category of women are shown in Table 2. The records of 66 infants were reviewed, 33 infants from each group. Major congenital malformations were not observed in any of the groups; however, seven minor congenital malformations and three other adverse foetal outcomes were seen. Minor congenital malformations were seen in 14.2% (3/21) of infants whose mothers used AEDs and had seizures compared to 16.7% (1/6) of infants whose mothers took AED but had no seizures. Minor congenital malformations were seen in 6.1% of foetuses in the control group. There were no minor congenital malformation seen in foetuses whose mothers had seizures but took no AED. A single-factor ANOVA analysis was performed to determine if there was any correlation between the AED use in pregnancy and the overall adverse foetal outcomes. A p-value of 0.04 was obtained at a confidence level of 95%. This suggests that there is a relationship between the AED use in pregnancy and the overall adverse foetal outcome.

Carbamazepine, phenytoin and valproic acid were the AEDs used in women whose infants were found with minor congenital malformation.

Most (45.5%) of the women who took AED during pregnancy for seizures had delivery via a caesarean section versus 33.3% of controls. The women who took AED for migraine had six cases that were analysed; the delivery record for the remaining case was unavailable. Within this group, 50% had induced vaginal delivery and 50% had spontaneous vaginal delivery.

Table 3 shows the maternal outcomes in all groups. Most adverse maternal outcomes were seen in women who did not take AEDs and did not have seizure. However, most of the adverse maternal outcomes seen in women who took AEDs were seen in those who took carbamazepine. The single-factor ANOVA analysis was performed to determine if there was any relationship

Table 2: Foetal outcomes in each category of infants

Category	Women used AED		Women did not use AED		Total
	Seizure	No seizure	Seizure	No seizure	
Foetal outcome					
Foetal Death	2	1	0	1	4
Intrauterine growth restriction	0	0	0	1	1
Microcephaly	0	0	0	1	1
Undescended testes	0	0	0	1	1
Premature birth	1	1	1	2	5
Umbilical hernia	2	0	0	0	2
Tapered superior helix of left ear	1	0	0	0	1
Over folded superior helix of the right ear	1	0	0	0	1
Posteriorly rotated low set ears	0	1	0	0	1
Slightly posteriorly rotated ear	1	0	0	0	1

AED = anti-epileptic drug.

Table 3: The maternal outcomes in each group of women

Category	Women used AED		Women did not used AED		Total
	Seizure	No seizure	Seizure	No seizure	
Maternal outcomes					
Uterine haemorrhage > 500 cc	4	0	2	6	12
Premature rupture of membrane	0	0	0	1	1
hyperemesis gravidarum	1	0	1	1	3
Abruptio placentae	0	0	1	0	1
mechanical rupture of membranes	7	3	1	12	23
Pre-eclampsia	0	0	1	2	3

AED = anti-epileptic drug.

between the AED use in pregnancy and the adverse maternal outcome. A *p*-value of 0.06 was obtained at a confidence level of 95%. This would suggest that there is no correlation between the AED use and the adverse maternal outcome.

DISCUSSION

This study sought to identify major and minor congenital malformations that may be present in infants who were exposed to AEDs in utero and the maternal outcomes that may be associated with their use. It was found that infants exposed to AEDs in utero had only minor congenital malformations and no major congenital malformations. This is a variation of what was seen in previous similar observational studies of women who were exposed to AEDs during pregnancy (1, 13, 19). This difference in outcome could be due to the small-sample size. The results are not unexpected, given the relatively few pregnancies complicated each year by AEDs use (20). As a result, multicentre design studies are the only feasible approach to gather unbiased data on a significant number of pregnancy outcomes (20).

In this study, the infants who were not exposed to AEDs had minor congenital malformations that were not seen in the infants exposed to AEDs in utero. This is not an unusual occurrence. Though previous studies reported that more malformations were seen in infants of mothers exposed to AEDs, they also reported that most of the major malformations identified were types of abnormalities that also occurred in infants whose mothers have not taken an anti-convulsant drug (19).

The difference in population could also affect outcome. Previous studies and registries were based on populations that were likely of mixed ethnicity, as they were of multicentre design involving women from different regions and countries (1, 2, 19). This study was composed primarily of women of the African descent. The Jamaican population is primarily of the African descent (90.9%) with people of mixed ethnicity making up 7.3% (21).

The use of the newer AEDs was not significant but as they become more available, it is expected that their use will increase among this population of patients and the foetal and maternal effects can then be appreciated.

Our study findings suggest that though MCMs are important adverse foetal outcomes to be aware of there are other significant adverse foetal outcomes that both the physicians and the pregnant women on AEDs are to anticipate and aim to mitigate against.

There were several limiting factors in this study. The study outcomes were hinged on the documented examination findings made by the attending physicians who were not following the guidelines recommended for assessing infants with in-utero exposure to AED/s. The New Born Services guideline is a recommended protocol for evaluating such infants (22). Furthermore, the physicians' documentation and their various opinions on the women was the only method of collecting information.

Regarding the anti-epileptic medications they were using, it is possible that non-compliance and adherence to prescribed medication by the mothers could also have impacted on the study outcome. Maternal complications of AEDs could possibly have been observed but not routinely documented by the obstetricians or the neurologists.

CONCLUSION

The study revealed that there are adverse effects, other than MCMs, of AED use in pregnancy on the foetal outcome. The adverse maternal outcomes were similar to those previously documented. It also demonstrates that the ongoing screening of mothers with epilepsy on AEDs is relevant to identify the foetal and maternal effects of AED use in pregnancy. It is, therefore, recommended that the guidelines for examining foetuses of mothers who use AED during pregnancy be followed so as to identify foetal anti-convulsant syndromes and, those infants that will go on to develop motor, language and cognitive abnormalities.

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AUTHORS' NOTE

SRG participated in the study design, oversaw data collection, conducted data analysis, wrote manuscript and approved final version. FG conceived paper, participated in the study design, oversaw data collection, critically review and approve final draft of manuscript. NJ oversaw data collection, critically review and approve final draft of manuscript. The authors declare that they have no conflicts of interest.

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