ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 15, Issue 10, 2022

Online - 2455-3891
Print - 0974-2441

Research Article

PREGNANCY OUTCOME AND EARLY DEVELOPMENT OF OFFSPRING IN WOMEN WITH EPILEPSY

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Received: 18 June 2022, Revised and Accepted: 26 July 2022

ABSTRACT

Objectives: The aim of the study was to evaluate the outcome of pregnancy and early development of offspring, in women with epilepsy (WWE) who were receiving and not receiving anti-epileptic drugs (AED).

Methods: Women with epilepsy who delivered in a teaching hospital (n=60), between November 2017 and October 2018, were identified from the delivery records (n=5202) and their infants (n=39) underwent developmental assessment by Baroda development screening test. Maternal epilepsy syndrome, AEDs during pregnancy, and other details were obtained from medical records and interview.

Results: Fourteen mothers received monotherapy, 15 polytherapy and 10 mothers were not taking any AED. There were four major congenital malformations (MCM) among 39 babies. Two were cardiac malformations; one was complex anomaly, caused death in neonate and other was ventricular septal defect (VSD). Both occurred in babies of mothers receiving clobazam in combination with oxcarbazepine and levetiracetam, respectively. There were two urological anomalies in babies unexposed to AEDs. When mothers were receiving monotherapy (14), normal Development Quotient score (DQ score) was observed in 11 babies, but low DQ score was observed in three. In the polytherapy group (15), normal DQ scores were found in five and low DQ in nine (one baby died neonatally). Among the group who were unexposed to AED (10), normal DQ score was found in eight, but low DQ in two (in the antenatal period mother of one of the low DQ babies reported frequent major seizures).

Conclusion: Clobazam therapy is a risk factor for developing MCM in babies of WWE. Oxcarbazepine, monotherapy or polytherapy, and Clobazam polytherapy are risk factors for low DQ scores in the offspring of WWE. Polytherapy and frequent seizures during pregnancy are also risk factors for low DQ scores. Widely used drugs which were considered safe demonstrated adverse effects in offspring. Even though sample size is small, it is a matter of concern and curiosity.

Keywords: Women, Epilepsy, Antiepileptic drugs, Oxcarbazepine, Clobazam, Pregnancy, Developmental outcome, Malformation.

 DOI: http://dx.doi.org/10.22159/ajpcr.2022v15i10.45575. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Mullers-Kuppers in 1963 reported association of AEDs with embryopathy and malformations in children of WWE on AEDs. In 1978, Phenytoin and Phenobarbitone were identified to cause craniofacial and limb anomaly in children borne to WWE. Gaetti *et al.* reported that AEDs can cause psychomotor retardation in offspring of WWE. The fact that AEDs can contribute to developmental and cognitive issues in children of WWE is known by 1990s [1]. Later, developmental issues are found with valproate also [2]. Higher AED dose, especially valproate, and polytherapy are found to be associated with adverse immediate fetal outcome and their subsequent cognitive development [3-5].

Managing pregnancy in WWE is challenging. The teratogenic effects of AEDs are to be balanced against efficacy to control seizures. Seizures in pregnancy cause significant morbidity, mortality, and poor fetal outcome. The target is seizure freedom on AEDs of least teratogenic potential before conception [6-8]. Thus, preconception counseling and planning of pregnancy is important. Multidisciplinary obstetric-epilepsy care and monitoring throughout antenatal period, labor, and post-partum period are to be provided to pregnant WWE. When these steps are taken, the outcome of pregnancy and health of offspring is good. Congenital malformations and impaired cognitive development in offspring of WWE on AEDs such as phenytoin and sodium valproate are well known.

We aimed to

1. Evaluate immediate fetal outcome in pregnant WWE on and off AEDs.
2. Assess development of infants of WWE using developmental quotient (DQ), by Baroda development screening test (BDST) [9].

METHODS

The case records of all women delivered from November 2017 to October 2018 at Department of Obstetrics and Gynecology, of a Government Teaching Hospital were screened after IRB clearance (IRB No.72/2018). All mothers with diagnosis of epilepsy were identified based on ILAE (International League against Epilepsy) official report: A practical clinical definition of epilepsy [10]. Women who had seizures in past 5 years or WWE on AEDs were included in the study.

Women with acute symptomatic seizures were excluded from the study.

The women were contacted (by post/telephone); invited for review/interview in the Neurology Department. Details of seizures, epilepsy syndrome, its treatment, detailed obstetric history, (antepartum and peripartum obstetric details), and development history of babies were obtained from the case records and interview. Their infants were evaluated with BDST [9] by the authors. BDST, developed by Phatak and Khurana in 1991, is a tool for assessing child development with sensitivity of 95% and specificity of 65%. It is used for the assessment of motor and mental development in infants of

30 months or younger. It is effective in identifying developmental delay in infants in Indian scenario.

After clinical examination, screening for MCM was done in Department of Radiology of the same institution. Cardiac malformations were confirmed by Department of Cardiology using echocardiography. For ureteric and renal malformations, screening sonograms were done at radiology department and confirmed by cystogram at Department of Urology.

Statistical analysis was done using the statcalc of Epi info7 (CDC Atlanta) online version.

RESULTS

Total 5202 case records were screened and 60 WWE identified. All 60 were invited for interview. Forty-one responded. Parity status of women was – Primipara – 16, Second para – 15, Third para – six, and Fourth para –four. Two mothers were excluded as acute symptomatic seizures: For one mother seizure was due to hypocalcemia secondary to hypoparathyroidism and for the other it was due to posterior reversible encephalopathy syndrome (PRES). There was history of nine abortions, one vesicular mole, and one ectopic gestation for the 39 WWE.

The mean age for WWE was 29.4±0.92 years (range 21–43 years). Thirty-seven (95%) were below poverty line (Income less than Indian Rupees. 27,000/year) and two were above it.

The educational qualification was higher secondary school level or below for 67.5% of WWE and their spouses.

Twenty-nine WWE (74%) took AEDs and 10 (26%) did not take them. During pregnancy, 5 (13%) mothers developed more than three seizures (in a month) and for 10 (26%), it was <3. There were 14 women in AED group who were seizure free. In the non-AED group (total 10), nine (23%) were seizure free (Last seizure being 4 years ago). One mother who was not taking AED developed frequent nocturnal seizures during pregnancy. There were 23 WWE who were seizure free for more than 1 year (nine off AEDs and 14 on AEDs).

All seizures were either generalized or secondarily generalized. Seizure frequency remained unchanged after delivery, except for the woman with frequent nocturnal seizures (not on AED), who became seizure free after initiating AEDs. Levetiracetam and clobazam were the most common AEDs used followed by carbamazepine and oxcarbazepine. Sodium valproate, phenytoin, phenobarbitone, lamotrigine, and topiramate were the other drugs used. The AEDs were used either as monotherapy or polytherapy with varying drug combinations.

Obstetric outcome

All WWE delivered live babies, but there was one neonatal death due to complex cardiac anomaly.

Developmental outcome of offspring

On assessing children's developmental status, between 8 and 18 months of age, for 24 children (63.2%), development was in the normal range (DQ ≥85) while 14 (36.8%) showed delayed development (DQ < 85) (Table 1 shows the developmental outcome).

In the group of WWE on AEDs (n=28), development was normal for 16 babies (57.1%), and 12 babies showed developmental delay. In the group WWE who were not on AEDs (n=10) during pregnancy, eight (80%) babies showed normal development and two developmental delay. (One mother was suffering from uncontrolled epilepsy and her baby showed developmental delay).

In the group of 14 mothers with generalized seizures, low DQ was observed in nine babies. In seizure free 23 (9+14) mothers, low DQ was observed for five babies. Generalized seizure in a pregnant WWE was a statistically significant risk factor for low DQ for the child (RR=3.08; 95% CI=1.28–7.38; p<0.007).

In monotherapy group of six WWE taking levetiracetam, development was normal for four children and delayed for two. Levetiracetam monotherapy was not found as a statistically significant risk factor for developmental delay in the offspring. When levetiracetam was used in combination with other drugs (nine WWE), for eight babies, DQ score was low and normal for one baby.

Clobazam was not given as monotherapy in the present series. When used in combination with other drugs, (in 12 WWE), there was one neonatal death due to complex cardiac anomaly and VSD was observed in another infant. When development of babies was assessed seven babies in this group showed delay. When clobazam exposure was considered as risk factor for both MCM and low DQ put together, the RR was 2.47 (95% CI=1.17–5.28; p<0.02). Clobazam exposure for cardiac anomaly alone was also statistically significant (p<0.03).

Five WWEs were taking oxcarbazepine; two were on monotherapy, three on combination therapy (One MCM, three developmental delay). Oxcarbazepine exposure was a risk factor for MCM and low DQ put together (RR=2.4. 95%; CI=1.25–2.60; p<0.04). Low DQ score was seen in one out of two children of monotherapy group which was found to be statistically significant (p<0.011). Antiepileptic usage and developmental outcome is shown in Table 2.

In AED polytherapy group, more than 50% babies showed developmental delay (Table 2). When combination of levetiracetam with clobazamwas used (three mothers), all three babies showed developmental delay. Oxcarbazepine-clobazam combination was used in two mothers. It resulted in one NND (50%) and one developmental delay (50%). There were four WWEs on polytherapy with three or more AEDs. Among them, developmental delay was seen in two babies and normal development in two.

Congenital malformations

There were four cases of congenital malformations (one complex cardiac defect resulting in NND exposed to oxcarbazepine and clobazam, one ventricular septal sefect (VSD) exposed to clobazam and two urological defects not on AEDs). Congenital anomalies and AEDs are shown in Table 3.

DISCUSSION

Although 41 out of 60 responded, only 39 WWE could be included in the study. The difference between responders and non-responders in observational study is not significant and bias could be nearly absent [11]. Thirty-eight children were available for assessment, as there was one child died neonatally due to complex cardiac anomaly.

The outcome of the pregnancy of 38 WWE and development of infants between 8 and 18 months is discussed. The authors assessed children using BDST, which is a tool to assess early development of infants. Investigations regarding anomalies were screened and confirmed by concerned specialists.

For the 14 children with developmental delay, nine mothers developed seizures and five did not during pregnancy. In normal development group of 24, seizures were reported by five. This association of developmental delay and maternal generalized seizures is statistically significant [12]. The cause of delayed development could be hypoxic ischemic changes secondary to reduced blood flow or prolonged bradycardia which occurs in fetus when mother develops seizures [13,14]. This emphasizes the significance of seizure control. For reducing maternal mortality and morbidity also, good seizure control is essential [15]. The immature brain is susceptible to widespread neuronal apoptosis secondary to a variety of insults including trauma and seizures [16]. It is found that frequent major seizures cause development delay and cognitive impairment [17]. For a healthy baby without congenital anomaly and good developmental outcome, seizure freedom with a single safe drug is best. Antiepileptic drug non-compliance causes increased mortality and other serious incidents in pregnant WWE [17].

Table 1: Antiepileptic drugs, developmental outcome of infants, and seizure status

S. No.	AED	DQ score	Developmental status	Seizure status
1	Levetiracetam, Topiramate	82	Delayed	Remission
2	None	82.3	Delayed	>3 in 3 months
3	Levetiracetam, clobazam	78.5	Delayed	>3 in 3 months
4	Oxcarbazepine, clobazam	41.2	Delayed	>3 in 3 months
5	Levetiracetam	78.5	Delayed	Remission
6	None	73.3	Delayed	Remission; not on AED
7	Levetiracetam, clobazam, Phenobarbitone, carbamazepine	64.2	Delayed	<3 in 3 months
8	Oxcarbazepine	75	Delayed	<3 in 3 months
9	Levetiracetam, clobazam	75	Delayed	<3 in 3 months
10	Levetiracetam	80.3	Delayed	<3 in 3 months
11	Levetiracetam, Oxcarbazepine, clobazam, carbamazepine	78.9	Delayed	>3 in 3 months
12	Phenytoin, clobazam	81.4	Delayed	<3 in 3 months
13	Sodium valproate, Levetiracetam	82.6	Delayed	Remission
14	None	88.4	Normal	Remission, not on AED
15	Carbamazepine, clobazam	92.8	Normal	Remission
16	Phenytoin, Phenobarbitone, clobazam	86.6	Normal	Remission
17	None	130	Normal	Remission not on AED
18	None	104.5	Normal	Remission not on AED
19	Levetiracetam	92.8	Normal	Remission
20	Oxcarbazepine	109	Normal	<3 in 3 months
21	Levetiracetam	90.9	Normal	Remission
22	Sodium valproate	103.3	Normal	Remission
23	Carbamazepine	89.2	Normal	<3 in 3 months
24	Carbamazepine	96.4	Normal	<3 in 3 months
25	Levetiracetam	92.3	Normal	Remission
26	None	88.4	Normal	Remission not on AED
27	Levetiracetam	91.1	Normal	<3 in 3 months
28	Sodium valproate	91.6	Normal	Remission
29	Carbamazepine, Lamotrigine, Levetiracetam	100	Normal	Remission
30	Clobazam, carbamazepine	100	Normal	>3 in 3 months
31	Carbamazepine	103.8	Normal	Remission
32	None	103.8	Normal	Remission not on AED
33	None	95.8	Normal	Remission not on AED
34	Sodium Valproate	95.8	Normal	Remission
35	None	89.2	Normal	Remission
36	Clobazam, Topiramate	105	Normal	Remission
37	None	95	Normal	Remission not on AED
38	Levetiracetam, clobazam	58.3	Delayed	Remission

Table 2: AEDs-developmental outcome and different drug regimen

AED	Normal DQ (number)	Normal DQ (%)	Delayed DQ (number)	Delayed DQ (%)	Total (N)
Levetiracetam monotherapy	4	66.7	2	33.3	6
Levetiracetam polytherapy	1	12	7	88	8 (one MCM)
Carbamazepine monotherapy	3	100	0	0	3
Carbamazepine polytherapy	2	40	3	60	5
Oxcarbazepine monotherapy	1	50	1	50	2
Oxcarbazepine polytherapy	0	0	2	100	2 (one NND)
Valproate monotherapy	3	100	0	0	3
Valproate polytherapy	0	0	1	100	1
Clobazam polytherapy	0	0	9	82	12 (one MCM and one NND)

Sub group analysis of individual drugs and their combinations shows some important observations which are statistically significant.

Oxcarbazepine

Total – Five; in combination, one cardiac MCM and NND were observed. In monotherapy for two, developmental delay occurred in one. In combination therapy for three, all showed developmental delay. Four women out of five developed problems.

In the present series, when oxcarbazepine was used in combination with clobazam, it resulted in NND due to complex cardiac anomaly. Case reports of cardiac anomalies of aortic stenosis, bicuspid aortic valve, patent ductus arteriosus and patent foramen ovale, and neonatal abstinence syndrome for oxcarbazepine are reported [18]. However, this finding is curious in that oxcarbazepine is considered as safe drug in pregnant WWE. Combination of oxcarbazepine and clobazam was reported by Veroniki *et al.* to be safe [19].

In the review article funded by Novartis, use of oxcarbazepine was looked up in different countries. In the monotherapy group, 6/248 (2.4%) and in polytherapy group 4/61 (6.6%) developed anomalies [20].

For the children of three women on polytherapy with oxcarbazepine, two showed developmental delay. It was found that impaired face recognition was seen in oxcarbazepine exposed infants [21]. In a network meta-analysis by Veroniki *et al.*, children exposed to oxcarbazepine developed autism, (OR=13.51; 95% CI=1.28–221.40) [19]. The findings of the present study, the occurrence of autism, and face recognition delay suggest clinical significance. Hence, oxcarbazepine warrants large scale studies for use of women in reproductive age group.

Table 3: Details of AED, seizure status and MCM

S. No.	Seizures in pregnancy	AEDs	MCM
1	Yes	None	Bilateral hydroureteronephrosis
2	Yes	Levetiracetam and clobazam	Ventricular septal defect
3	None	Oxcarbazepine and clobazam	NND due to complex cardiac anomaly
4	None	None	Renal cortical defects and hydroureteric reflux

Clobazam

It was used only in polytherapy. Total – 12; two cardiac MCM, one died neonatally, and the other child developed VSD.

Among the alive 11 infants, two were normal and nine showed developmental delay. Ten children developed problems. Neonatal death due to complex cardiac anomaly was found when clobazam was combined with oxcarbazepine. Malformation risk due to clobazam in monotherapy group was found to be 22% [4]. In the meta-analysis by Veroniki *et al.*, the odds for MCM risk with clobazam were 3.55 and for growth retardation, odds were 4.47 [19].

Buchanan reported in a prospective study of 8-year follow-up, among three pregnant women on clobazam polytherapy, one developed persistent fetal circulation [22].

Embryofetal mortality and incidences of fetal skeletal variations were increased with clobazam use in pregnant animals. The product monograph revealed not much teratogenic effects in mice and rats in low dose, but cleft palate was observed at high dose. In rabbits, minor congenital anomalies were reported at low dose, while hydrocephalus and umbilical hernia were reported in higher dose. Clobazam causes fetal malformations by toxicological studies [23,24].

Regarding developmental outcome, data are scarce. However, in an uncontrolled study where clobazam was given to three pregnant WWE, one child developed attention deficit disorder [22]. Clobazam use as AED in pregnancy was associated with risk of intrauterine growth retardation and premature birth [19,25]. All these and present findings do not favor clobazam.

Levetiracetam

Total – 14; six monotherapy and eight polytherapy. One child developed MCM in combination with clobazam. On polytherapy, there were seven developmental delay and two developmental delays on monotherapy. Nine women developed problems.

Ellen *et al*. found that in levetiracetam monotherapy group, MCM was not significant. It was significant in the poly therapy group [26]. Antiepileptic regimen determined MCM risk of polytherapy; low when lamotrigine was combined and high when valproate was used. In the present series, MCM developed when combined with clobazam, while none was observed in levetiracetam monotherapy. Many studies found levetiracetam monotherapy to be safe in pregnancy, with risk for MCM similar to that of AED unexposed women, but polytherapy increased the risk [26,27].

Shallcross found, with regards to development, children of WWE on levetiracetam got higher scores, similar as that of unexposed children. However, 8% did have low DQ scores (DQ score of <84) [28]. Regarding developmental effects on levetiracetam monotherapy and polytherapy, studies are warranted using larger number of subjects.

Interestingly children exposed to carbamazepine [29] and sodium valproate in monotherapy did well. The dosage used was small, being <400 mg/day. Developmental effect of Valproate is dose dependent [30].

When the mother is on polytherapy, more than 50% of infants showed developmental delay. This was seen earlier also when polytherapy was associated with impaired verbal and non-verbal IQs in both human and animal studies. Overall polytherapy outcome was worse than monotherapy [3].

WWE not on drugs, in remission

Fetal outcome for WWE in remission (not on AED) was good for eight out of 10. Two showed developmental delay. For one child, mother developed uncontrolled epilepsy during pregnancy, while for the other, no risk was identified.

Limitation

Sub group analysis using individual drugs is of small sample size and may require larger studies. There is low level of response to participation (68%).

CONCLUSIONS

Newer AEDs may cause potential harm, if not used with utmost care in WWE who are planning to get pregnant. The AEDs, clobazam, and oxcarbazepine either as monotherapy or polytherapy should be used with caution among WWE until large studies prove them to be without harm. Outcome of levetiracetam monotherapy is good. When planning for levetiracetam combination therapy, the drug to be combined should be chosen with care.

Status of epilepsy control, with regard to major seizures, is an important predictor for developmental outcome, known earlier was reconfirmed. Developmental outcome for polytherapy scores poor on comparison to monotherapy.

ACKNOWLEDGMENT

The authors would like to thank Professor (Dr) Sanjeev V Thomas, Trivandrum for the valuable advice.

AUTHORS' CONTRIBUTION

Conception of idea, literature review, data collection, analysis, and manuscript writing: Beena Vasanthy. Data collection, literature review, and manuscript writing: Maria Rose Dominic. Statistical analysis and manuscript writing: Vijayan Chandrathil Parameswaran Nair.

CONFLICTS OF INTERESTS

Nil.

AUTHORS FUNDING

State Board of Medical Research, Medical College Kottayam. Kerala Association of Neurologists. Ethical Committee clearance: IRB no.72/2018 Government Medical College Kottayam, Kerala, India.

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