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Original Research Article

## Fetomaternal outcomes in pregnancy complicated by epilepsy- a retrospective study

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### ABSTRACT

**Background:** This study is conducted to find out possible course and complications of epilepsy and its treatment in mother and fetus as many women will be anxious regarding this high-risk condition.

**Methods:** This is a retrospective study conducted in department of obstetrics and gynaecology, AIMS Kochi from 2012-2019. Out of a total of 7045 deliveries during that period, we identified 64 patients with epilepsy complicating pregnancy. Antepartum, intrapartum and postpartum details of 57 patients whose data was available in electronic medical records was collected and analysed using SPSS 17 software.

**Results:** In this study we noted that the incidence of epilepsy was 0.009%. the 50% of patients were in 25-30 years age group. More than 98% were on long term antiepileptic drugs. Majority were on monotherapy, most commonly on leviteracetam and were well controlled with monotherapy. The 38.5% had recurrence of seizures during pregnancy, mostly in latter half of pregnancy. Patients with seizure free interval of 9 months prior to pregnancy did not have any further epilepsy episodes. The incidence of other medical and obstetric complications was found to be similar to general population. There was 10% incidence of IUGR and fetal anomaly.

**Conclusions:** The seizures were well controlled with monotherapy and we found that generally pregnancy and delivery is well tolerated and overall neonatal outcomes were good.

**Keywords:** Epilepsy, Seizure, pregnancy, Leviteracetam

### INTRODUCTION

Epilepsy is the recurrent unprovoked seizures resulting from excess neuronal discharge. It is the most common neurological condition in pregnancy which needs medical treatment.<sup>1</sup> Since 40% of women are in the reproductive age it is fairly common to see epileptic patients embarking on pregnancy. Although most of the pregnancies progress without complications it is considered as a high-risk pregnancy. Recent advances in antiepileptic medications have helped to limit the seizure frequency and duration. But still, it is not uncommon to see severe forms of epilepsy like status epilepticus which can cause much maternal morbidity. The risk of fetal complications is twice common in patients with epilepsy than in general

populations-may be because of use of anti-epileptic drugs or direct effect of epilepsy causing hypoxic insult to placenta.<sup>2</sup>

There are significant variations in the reported fetomaternal complications across various populations we conducted this study to analyze the outcomes of pregnancy complicated by epilepsy in our institution.

### METHODS

This study was conducted in the department of obstetrics and gynecology, Amrita institute of medical sciences, Kochi from 2012 to 2019.

It is a retrospective descriptive study in which the data of all booked antenatal patients diagnosed with epilepsy was collected from the labor records and electronic medical records.

Out of the 7045 deliveries during these periods we identified 64 patients with epilepsy. Since the follow up data was not available for 7 patients they were excluded from the study. All these patients were taking 5 mg of folic acid and neurology opinion.

All patients underwent anomaly scan and growth scan and regular antenatal checkup.

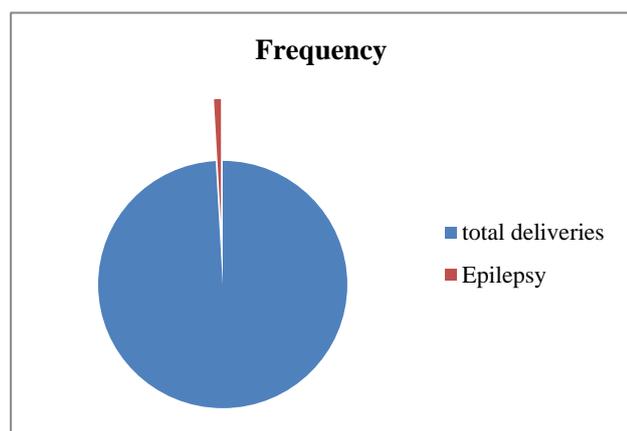
The details of these 57 patients with epilepsy-like age, parity, type, years of seizure medications, seizure free interval before pregnancy, drugs used in pregnancy (monotherapy or polytherapy), seizure episode during pregnancy in each trimester, coexisting medical disorders like gestational diabetes, pregnancy induced hypertension and obstetric complications like preterm labor, PPRM, antepartum hemorrhage, mode of delivery, fetal outcomes like anomalies, birth weight; were collected.

All babies were given injection vitamin K IM at birth as part of routine IAP protocol and also started breastfeeding soon after birth.

Both maternal variable and fetal variable were presented in frequency and percentage using SPSS version 17.

## RESULTS

Out of the total 7044 deliveries over 8 years (2012-2019) in our institution we identified 64 patients with epilepsy complicating pregnancy thus giving a very low incidence (0.009) (Figure 1).



**Figure 1: Frequency.**

Out of 57 patients, majority were in 25-29-year age group (50.9%), 59% were multigravidas and 47.4% patients were on AED for 10-20 years. Only one patient was not on any AED as her last seizure episodes was 7 years back, hence the drug was withdrawn (Table 1).

**Table 1: Sociodemographic analysis.**

Variables	Frequency	Percentage (%)
<b>Age (Years)</b>		
18-24	14	24.6
25-29	29	50.9
30-35	11	19.3
>35	3	5.3
<b>Parity</b>		
Primi	23	40.4
Multi	34	59.6

Looking into the type of seizures it was noted that 77 % patient had generalized tonic clonic seizure (44/57), 18 % were diagnosed with myoclonic seizures, 2 cases (3.5 %) were of complex partial seizures and status epilepticus each.

Of the 57 patients only 26.3 % (15/57) had received multiple medications for seizure control. In majority (77.7%) were controlled with single AED like levetiracetam (49%), benzodiazepine (26%) and other drugs like topiramate (17%).

**Table 2: Epilepsy characteristics.**

Variables	Frequency	Percentage (%)
<b>Duration of seizures medications (Years)</b>		
<10	20	35.1
10-20	27	47.4
20	9	15.8
No AED	1	1.8
<b>Type of seizures</b>		
GTCS	44	77.8
Myoclonic	1	1.8
Complex partial	2	3.5
Status epilepticus	2	3.5
Others	8	14
<b>Seizure free interval prior to pregnancy (years)</b>		
<1	22	38.5
>1	28	49.1
Not available	7	12.4

During the antenatal period 22 patients (38%) had seizure episodes with comparable incidence in all three trimesters- 6 in 1<sup>st</sup> trimester (24%), 8 each in 2<sup>nd</sup> and 3<sup>rd</sup> trimester (36% each). We had one patient on polytherapy who had multiple uncontrolled seizures in all 3 trimesters with cause for same not identified and another patient who was on monotherapy had seizures in 2<sup>nd</sup> and 3<sup>rd</sup> trimester. The seizures subsided spontaneously postpartum after altering the dose of drug. 2 patients had intrapartum seizures and none happened in postpartum.

Of the patients who had seizures during the antenatal period 17.5% patients needed revision and hiking anti-epileptic medications (Table 3).

**Table 3: Epilepsy characteristics in pregnancy.**

Variables	Frequency	Percentage (%)
<b>Drug treatment</b>		
No drugs	1	1.7
Monotherapy	41	71.9
Levipil	20	48.7
Benzodiazepines	10	24.3
Carbamazepine	4	9
Others (like divalproex, lamotrigine)	7	17
Polytherapy	15	26.3
<b>Incidence of seizures in pregnancy</b>		
Antepartum	22	38.5
1 <sup>st</sup> trimester	6	27
2 <sup>nd</sup> trimester	8	36
3 <sup>rd</sup> trimester	8	36
All 3 trimesters	1	
Intrapartum	2	3
Postpartum	0	
<b>Pregnancy co-morbidities</b>		
GDM	4	7
PIH	3	5
<b>Change in dose/medications</b>		
Needed	10	17.5
Not needed	47	

On analysis of maternal data, 3 patients developed pregnancy induced hypertension and 4 developed GDM. None of the patients had obstetric complications like antepartum hemorrhage, PPRM or stillbirth.

Over a half (54 %) of patient went for cesarean section because of various indication, most common being previous LSCS. The 84.3% were term deliveries while 15% were preterm deliveries.

**Table 4: Fetal characteristics.**

Variables	Frequency	Percentage (%)
<b>Congenital anomalies</b>	6/57	10.52
<b>IUGR</b>	7/57	10
<b>Gestational age at delivery</b>		
Pre term	9	15.7
Term	48	84.3
<b>Mode of delivery</b>		
Normal	26	45.6
LSCS	31	54.4
<b>Sex of the baby</b>		
Male	35	61.4
Female	22	38.6
<b>Birth weight (kg)</b>		
<2	6	10.5
2-2.5	7	12.3
>2.5	44	71.2

Out of 57 babies born 35 were males (61%) and 22 were females. Majority 71.2% weighted average size of more than 2.5 kg while 10.5% were less than 2 kg (Table 4).

## DISCUSSION

The 2.5 million Women in India suffer from epilepsy and 25% are in reproductive age group. Hence, addressing epilepsy in pregnancy is important.

The review of literature suggested preference of monotherapy over polytherapy during pregnancy.<sup>3</sup> This is due to decreased risk of side effects and congenital anomalies due to synergistic effect of both the drugs. Even in our study, majority (77%) were well controlled with monotherapy with drugs like leviteracetam, benzodiazepines. Polytherapy was resorted to only when there was failure of monotherapy at maximum permissible doses.

As per study by Robinson et al epilepsy has been associated with increased rates of cesarean section although the indication is not clear. Epilepsy itself is not an indication for cesarean section.<sup>4</sup> The study consisted of 59% multigravidas and the rate of cesarean delivery in our study also of almost 54%. The most common indication identified was previous cesarean with mobile head.

There is insufficient evidence of change in frequency of seizure episodes during pregnancy, as per American association of neurology, however Monead study stated that women who had a 9 month seizure free interval prior to pregnancy were less likely to have seizure episodes during pregnancy.<sup>5</sup> Recent study showed, use of leviteracetam is associated with increased seizure free interval and better outcomes while lamotrigine and carbamazepine had similar results.<sup>6</sup> In our study, majority of the patients (49.1%) had seizure free period for more than 1 year prior to pregnancy and had hence had seizure free antenatal period.

The study of neurological diseases in pregnancy stated incidence of intrapartum seizure to be around 3-4%.<sup>7</sup> In our study, we had 2 patients who had intrapartum seizures (3%). Both were managed with IV leviteracetam.

There was one patient who was on polytherapy and had multiple episodes of epilepsy in ante partum and intrapartum period. This may be due to non-adherence to antiepileptic medications. One patient had multiple seizure episodes in second and third trimester; this could be due to change in therapeutic levels of leviteracetam in pregnancy, which ideally needs to be monitored as seen in study by Mahajan et al.<sup>8</sup> However, RCOG does not currently recommend routine serum antiepileptic drug monitoring because of lack of its evidence on control of seizures.<sup>7</sup>

In previous studies like by Goel et al there was 24.3% incidence of PIH and 2.7% incidence of GDM with epilepsy.<sup>9</sup> Overall it has been reported that there is higher

incidence of preeclampsia in patients with epilepsy complicating pregnancy especially on lamotrigine and carbamazepine.<sup>10</sup> In our study, though the incidence of GDM was comparable to around 7%; we got a lower incidence of PIH of around 5% only. It could be related to use of leviteracetam; however, there is no proven study.

Due to increase in clearance rate of drugs during pregnancy, there is increased need for changing drug dosage and opting for higher doses. Almost 45% of patients needed change in drug dosage in our study.

Postpartum, risk of epilepsy is 1-2% but in our study no incidence of postpartum seizure was noted.<sup>7</sup> This may be due to strict adherence to the antiepileptic medications.

Major malformations have been associated with use of valproate as a monotherapy or polytherapy so should be avoided. Antiepileptic like lamotrigine and levetiracetam even in combination are equivalent to monotherapy in safety. Among newer drugs, lamotrigine is safest during pregnancy though when compared to general population still higher risk of congenital malformations is there. Topiramate has intermediate risk of malformations with facial/palate cleft. Folic acid supplementation is recommended preconceptionally and during pregnancy at a minimum dose of 0.4 mg/day (4 mg/day if family history of neural tube defect, or on valproic acid, carbamazepine, or gabapentin).<sup>5</sup>

Epilepsy itself does not significantly increase risk of major congenital malformation. It is noted that risk of congenital malformation in women taking antiepileptic drug is 10% compared to general population.<sup>11</sup> In our study, congenital anomalies were seen in 10.5% of the study group most of which were correctable cardiac anomalies like SVT, VSD.

As per previous studies, there is conflicting data on evidence of preterm delivery and SGA fetuses among women on antiepileptic and those without. In case of preterm deliveries, the cause has been attributed to seizure itself.<sup>12</sup> There is twofold increase in SGA babies amongst women on antiepileptic drugs compared to those not on any drugs.<sup>13</sup> In our study we had 10% babies with growth restriction and low birth weight.

### **Limitations**

In this retrospective study, data was collected from hospital records, hence few of the data was missing. There was loss to follow up and majority of patients studied in this were multigravidas. Because of small number of cases spread over a long period the effect of antiepileptic drugs could not be evaluated individually. Cases were managed by different consultants resulting in non-uniform protocols. There was a lack of other neonatal data like duration of NICU stay, management protocols and long term follow up. Hence targeted additional prospective study is needed. Despite these limitations we believe it will

be useful for clinicians to counsel their patients about the prospective overall outcomes and management.

### **CONCLUSION**

Pregnancy complicated by epilepsy is definitely a high-risk condition that needs multidisciplinary and careful management. Pre-conceptional counselling is very important in such patients and they should be counselled about optimising the antiepileptic medications, importance of compliance and adhering to follow up to see for change of dose. Pre-conceptional counselling and folic acid is recommended for all women on antiepileptic medications at 0.4mg/day. If family history of neural tube defect is present, recommended dose is 4 mg/day. Monotherapy for epilepsy treatment has been associated with better fetomaternal outcomes in pregnancy. However, due to increased drug clearance in pregnancy, there is frequent need for changing of drug dosage. Lamotrigine and levetiracetam have been shown to be safest out of all the antiepileptic drugs in pregnancy in terms of fetal malformations and adverse fetal outcomes like NICU admission. Overall, generally pregnancy and delivery are well tolerated and overall neonatal outcomes are good if patient has a seizure free period before conception and epilepsy is well controlled.

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