

Maternal and fetal outcomes of women with epilepsy: study from a tertiary care center in India

Abstract

Introduction: Epilepsy is the second most common neurological disorder in pregnancy. Most women with epilepsy have uneventful pregnancies but many studies have shown increased maternal and fetal complications. **Material and Methods:** We retrospectively analyzed maternal and fetal outcomes of 59 women with epilepsy, taking a control group of 234 women with uncomplicated pregnancies, at a tertiary care center in India, over a period of 5 years. We have also compared outcomes of women who had epilepsy due a known cause and the ones with epilepsy of unknown origin; and outcomes in women on first and second generation AEDs. **Results:** There was no significant difference in the obstetric outcomes of the patients in the two groups. Risk of major congenital malformations was significantly higher in the patient group as compared to the control population ($p=0.01$); other fetal complications did not show any significant difference. Women who had a known cause for their seizures had a higher incidence of seizure episodes in pregnancy (38.8% vs 24.4%), but this was not statistically significant. Women who were on second generation AED had a higher incidence of seizures during pregnancy (42.8% vs 30%) as compared to the ones on first generation, although not statistically significant. **Conclusion:** As almost one fourth of patients affected with seizures are women of reproductive age group, preconceptional counseling forms an important part of their management. Although most women might have uneventful pregnancies, the risks to the fetus associated with drug exposure needs to be weighed against the risk of maternal disease.

Keywords: epilepsy, pregnancy, maternal, fetal, antiepileptic drugs, complications, congenital malformation

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Introduction

Second only to headache as the commonest neurological disorder in pregnancy, epilepsy has a prevalence of 0.3-0.7%.¹ Most of the females with epilepsy have uneventful pregnancies^{2,3} but many studies have shown that epilepsy can cause increased complications in the form of abortions, bleeding in early pregnancy, nausea and vomiting, preterm labor, hypertension, intrauterine growth restriction, intrauterine foetal demise and increased caesarean delivery rates.⁴⁻⁶ The fetus is at a much higher risk of teratogenicity due to the antiepileptic drug (AED) intake by the mother.⁷ Due to increased drug metabolism and clearance, and increased volume of distribution associated with pregnancy, serum concentration of drugs decrease, leading to higher frequency of seizures in pregnancy necessitating an increase in the dosage of AED.⁸ In this study we have analyzed the obstetric and fetal outcomes of women with epilepsy. We have also compared outcomes of women who had epilepsy due a known cause and the ones with epilepsy of unknown origin; and outcomes in women on first and second generation AEDs.

Materials and methods

This was a retrospective study conducted in the department of Obstetrics and Gynecology, All India Institute of Medical Sciences (AIIMS), New Delhi. Out of 4319 females who delivered in one particular unit of the department from May 2008 to May 2013 (5 years), 59 i.e. 1.3% of the females had epilepsy. We also took a control group of 234 pregnant females of matched age, with uncomplicated pregnancies.

Clinical details of all patients were recorded. This included age,

parity, obstetric history, time since diagnosis of epilepsy, type of seizures, underlying neurological lesion, anti-epileptic drug (AED) and peri-conceptional folic acid intake. Details of obstetric ultrasounds and previous/present neurological imaging were taken. Any obstetric, fetal or neurological complication was noted.

Details of AED (first or second generation), need for increase or decrease in the dose of AED, change in AED, conversion from monotherapy to polytherapy during pregnancy, seizure episodes in pregnancy and labour were recorded. Further outcomes were compared between patients who were on first vs second-generation antiepileptics and between those who had epilepsy with known cause vs epilepsy of unknown origin.

Data has been presented as mean \pm SD. Statistical significance was accepted at the 95% confidence level ($P < 0.05$). Chi-square and Student's t test were used for statistical analysis.

Results

The *baseline clinical features* of the study population have been shown in Table 1. Almost 60% of the females (35/59) were not taking folate tablets pre-conceptionally, despite being on anticonvulsants.

Antiepileptic therapy

AED that were taken by the study population have been summarized in Table 2.

Maternal outcomes

Mean gestational age at the time of delivery was 37 weeks 2 days. Majority (46) patients delivered at term (37-40 weeks). Vaginal

delivery was seen in 36(61%) of the mothers. Forceps application was seen in 2(3%) of the patients. 21(36%) delivered by cesarean section. All cesareans were performed for obstetrical indications. 10(48%) cesareans were done for fetal bradycardia, 3(14%) on patients request, 2(9%) for Meconium stained liquor and contracted pelvis each and 1(5%) each for arrest of cervical dilatation, failed induction, breech presentation and eclampsia. In the control group, 42 patients (18%) delivered by cesarean section, but this difference in the rates of cesarean section was not significant ($p=0.44$)

Table 1 Baseline clinical features of the patients

Age (in years) Mean±S.D	26.47±4.3
Obstetric History	
Primigravida	28(47.4%)
Multigravida	31(52.6%)
Pervious abortions	17(28.8%)
Previous Malformations	2 (3.3%)
Time Since Diagnosis of Epilepsy(in years) Mean ±S.D	6.1±4.1
No. of Women where Epilepsy was Diagnosed during Pregnancy	7(11.8%)
Epilepsy-Unknown Etiology	41(69.5%)
Epilepsy-Known Etiology	18(30.5%)
Neurocysticercosis	7
Head Injury	6
Tuberculoma	3
Tubercular Meningitis	1
Cortical Vein Thrombosis	1
Type of Seizure	
Generalized Tonic Clonic Seizure	55(93%)
Focal with Altered Consciousness	3 (5%)
Focal with Preserved Consciousness	1 (2%)

Table 2 Antiepileptic therapy

Antiepileptic therapy	No. of patients
No. of Patients not on AED	3 (5%)
Monotherapy	37 (63%)
Carbamazepine	15 (25.4%)
Valproate	9 (15.2%)
Phenytoin	6 (10%)
Levetiracetam	6 (10%)
Lamotrigine	1 (1.6%)
Polytherapy	19 (32%)
2 drugs	13 (22%)
3 drugs	6 (10%)
Polytherapy with Valproate	10 (16.9%)
Valproate Therapy (Mono & Poly)	19(32.2%)

Table Continues...

Antiepileptic therapy	No. of patients
Newer Antiepileptic Drugs	No. of patients 24(40.6%)
Levetiracetam	14 (23.7%)
Oxcarbazepine	5(8.4%)
Lamotrigine	3(5%)
Topiramate	2(3.4%)
Other Drugs	
Clobazam	7(11.8%)
Clonazepam	3 (5%)
Phenobarbitone	3 (5%)

Obstetrical complications

The maternal and fetal complications have been detailed in Table 3. There was no significant difference in the rate of maternal complications when compared with those seen in the control group.

Table 3 Obstetrical complications

Maternal complications	Mothers with epilepsy (n=59)	Control population (n=234)	P value
Gestational Diabetes	5(8.4%)	29(12.3%)	0.64
Intra Hepatic Cholestasis Of Pregnancy	5(8.4%)	15(6.4%)	0.57
Hypothyroidism	3(5%)	19(8.1%)	0.58
Oligoamnios	3(5%)	8(3.4%)	0.7
Gestational Hypertension	2 (3.3%)	12(5.1%)	0.74
Preclampsia	2 (3.3%)	4(0.1%)	0.6
Eclampsia	1(1.6%)	0(0%)	0.2
Atonic PPH	1(1.6%)	7(2.9%)	1
Fetal Outcomes			
IUGR	8(13.5%)	22(9.4%)	0.47
Intra Uterine Demise	1(1.6%)	6(2.5%)	1
Congenital Malformations	5(8.4%)	3(1.2%)	0.01

$p<0.05$ was taken as significant.

Pregnancy and seizures

Only a single mother had seizure episodes during labor, while 17(28.8%) of the mothers had one or more episodes of seizure in pregnancy, as shown in Table 4. There were no serious seizure related injuries to the mothers. Three (5%) of the mothers who developed seizures for the first time during pregnancy and were started on AED. Eight (13.5%) of the mothers needed an increase in the dose of medication and 6(10%) needed addition of another AED to control seizures during pregnancy. None of the mothers were switched from poly to monotherapy; none had a decrease in the dose of AED.

Table 4 Pregnancy and seizures

	No. of patients
Seizure Episodes in Pregnancy	17(28.8%)
Seizure Episodes in Labor	1(1.6%)
Antiepileptic Drugs Started in Pregnancy	3 (5%)
Increase in Dose of Antiepileptic Drugs	8 (13.5%)
Decrease in Dose of Antiepileptic Drugs	0
Addition of Another Drug	6 (10%)
Change from Poly to Monotherapy	0

Fetal outcome

26(44%) of the newborns were in the weight bracket of 2.5-3.0Kg. Of the 59 babies, 8(14%) had birth weights less than 2.5Kg and 6(10%) had birth weights more than 3.5Kg. There was one intrauterine fetal demise. The mother was a 23 year old primigravida with a history of epilepsy since last 7 years. She was on two AED (Carbamazepine 200 mg BD and phenobarbitone 60 mg BD). She was a non-compliant patient with irregular follow-ups, had 9 episodes of seizures in this pregnancy. The patient had been advised an increase in the dose of AED, but did not comply. She presented at 29 weeks with an IUD, was induced and delivered an 848gm macerated baby. There was no difference in the rates of growth restriction and intrauterine deaths between the patient and control group (Table 3).

Congenital malformations

Out of the 59 mothers with epilepsy who delivered with us, 5(8.5%) newborns had congenital malformations as outlined in Table 5. One (20%) of these 5 mothers was on monotherapy, rest 80% were on polytherapy with two antiepileptics, and 3(60%) were on polytherapy with valproate. Of the total mothers taking valproate, 3 out of 19(15.5%) had babies with malformations. One out of 37 (2.7%) mothers who were on monotherapy with any AED had babies with malformation and 4 out of 19 (21%) mothers on polytherapy had babies with malformations (Table 3). In the control group only 3(1.2%) of the mothers delivered babies with congenital malformations (one baby with hypoplastic left heart syndrome, and two with Congenital diaphragmatic hernia). Two of the study population group had had previous babies, delivered at term with malformations. One of them had a baby with menigomyelocele and the other had a baby with hydrocephalous.

Table 5 Congenital malformations

No.	Malformation	Antiepileptic therapy	Folic acid intake	
			Pre	Post
1	Tetralogy of Fallot (TOF)	Valproate & Phenytoin	No	No
2	Hypospadias	Valproate & Carbamazepine	No	Yes
3	Posterior Urethral Valve	Phenobarbitone & Levetiracetam	Yes	Yes
4	Cleft palate	Valproate & Clonazepam	Yes	Yes
5	CCAM	Carbamazepine	Yes	Yes

AED, antiepileptic drug; TOF, tetralogy of fallot; CCAM, congenital cystic adenomatoid malformation

Comparison of outcomes in women with epilepsy of unknown etiology and women with epilepsy with known etiology (Table 6)

Table 6 Comparison of outcomes in women with epilepsy of unknown etiology and women with epilepsy of known etiology

	Epilepsy – unknown aetiology (n=41)	Epilepsy-known aetiology (n=18)	P Value
Seizure During Pregnancy and Labor	Pregnancy -10 (24.4%) Labor-1 (2.4%)	Pregnancy -7 (38.8%) Labor-0 (0%)	0.35
Increase in Antiepileptic Dose	4 (9.7%)	4 (22.2%)	0.23
Polytherapy	15 (36.5%)	4 (22.2%)	
2 drugs	12(29.2%)	1(5.5%)	0.56
3 drugs	3 (7.3%)	3 (16.6)	
Congenital Anomalies	4 (9.7%)	1 (5.5%)	1
Preterm Delivery	4 (9.7%)	3(16.6%)	0.66
Birth Weight<2.5Kg	10 (24.4%)	6 (33.3%)	0.54
Still Birth	1(2.4%)	0(0%)	1

Kg: Kilogram p<0.05 was taken as significant

Patients who had a known cause for their seizures had a higher incidence of seizure episodes in pregnancy (38.8% vs 24.4%), but this was not statistically significant. Similarly need for increase in the dose of AED was higher in the group with established cause for seizures (22.2% vs 9.7%), but this again was not statistically significant. Rates of congenital anomalies, preterm delivery, and birth weight less than 2.5Kg and Stillbirth rates were not significantly different between the two groups.

Comparison of outcomes in women on first generation antiepileptics vs women on second generation antiepileptics (Table 7)

Table 7 Comparison of outcomes in women on first generation antiepileptics vs women on second generation antiepileptics

	1 st Generation antiepileptics (n=30)	2 nd generation antiepileptics (n=7)	P value
Seizure During Pregnancy	9 (30%)	3 (42.8%)	0.65
Increase in Antiepileptic Dose	5 (16.6%)	3 (42.8%)	0.15
Congenital Anomalies	1 (3.3%)	0 (0%)	1
Preterm Delivery	6 (20%)	0 (0%)	0.57
Birth Weight<2.5 Kg	8 (26.6%)	1 (14.2%)	0.65

p<0.05 was taken as significant.

Women who were on second generation AED had a higher incidence of seizure episodes during pregnancy (42.8% vs 30%) as compared to the ones on first generation, although not statistically significant. This probably could be due to better potency and seizure

control of the first generation AED. 42.8% women on monotherapy with second generation AED needed an increase in the dose of the medication to remain seizure free as compared to the ones of first generation AED (16.6%), although again not statistically different. Rates of congenital anomalies, preterm delivery, birth weight less than 2.5Kg were not significantly different between the two groups.

Discussion

Pregnancy with epilepsy poses a serious challenge, to both the obstetrician and the neurologist. With the physiological alterations in drug metabolism in pregnancy and increased risk of seizures, it might necessitate an increase in the dose of the AED, but the risk of teratogenicity with the same might be something for the neurologist to worry about.

More than two thirds (71.2%) of the women in our study did not have seizure episodes in pregnancy. This was similar to what has been seen in the recent studies.^{9,10} The risk of increased obstetric complications in women with epilepsy still remains a matter of debate, with many reports in literature stating the opposite. Apart for the significant increase in the risk of congenital malformations, we in our study did not find any increased risk of maternal or fetal complications as compared to the control group.

Majority of our study population was on monotherapy (63%). Almost 40% of the patients were taking the second generation AED, with Levetiracetam being the most commonly prescribed newer drug (23.7%). But despite the established risk of teratogenicity with valproate, almost one third (32.2%) of our study population was still on valproate, either as monotherapy or a part of polytherapy. This could be because our institute serves as a referral center and many a times we get late referrals where the woman has already taken valproate in the periconceptional and early weeks of pregnancy. This highlights the importance of preconceptional counselling and need for the neurologists to step in early, avoid prescribing valproate to women in the reproductive age group as far as possible and change over to safer drugs if needed.

The commonest malformation associated with AED intake have been seen to be neural tube defects, orofacial defects, diaphragmatic hernia, gastrointestinal tract atresia, cardiac defects, craniosynostosis and hypospadias.^{9,11-14} The 8.5 % risk of congenital malformation observed in our study is higher than the 7.1% risk that has been seen in a recent meta-analysis of 79 studies by Meador et al.¹⁴ We observed a 15.5% risk of malformation with valproate exposure as compared to 10.73% observed in the study. The risk of malformation with monotherapy in our study was 2.7% and 21% with polytherapy. The same meta-analysis has observed 11.4% and 14-25% risk of teratogenicity with polytherapy with two and more than two drugs respectively. In general, valproate should preferably be avoided in women of reproductive age group.¹⁴

It is a well-established fact that most AED, especially valproate are associated with lower folate levels in the body^{15,16} thus increasing the chances of having foetal neural tube defects. Thus one could have hypothesized that supplementation of folate would counteract the teratogenic effects on the exposed infants.¹⁷ However recent evidence fails to support the same. Many reports¹⁸⁻²⁰ demonstrated no decrease in the risk of NTD of valproate by supplementation of folates.

Data on second generation antiepileptics in pregnancy, apart from lamotrigine, is very limited. We observed a higher incidence of seizures and need for increase in dosage of AED in the study

population who were on second-generation antiepileptics as compared to the group taking the older AED. This could be related to altered pharmacokinetics and increased renal clearance of the second-generation drugs in pregnancy.²¹ According to the EURAP data²² Lamotrigine and levetiracetam (LEV) have the lowest risk of congenital malformations (2.9% and 1.6% respectively) while topiramate has been shown to have a significantly higher risk (6.8%). In our study, we did not find any significant difference in the rate of malformations between the two groups.

In our study we have also compared outcomes of women on first and second-generation antiepileptic drugs. Females on first generation antiepileptics had a lesser incidence of seizure episodes during pregnancy. More females taking the newer antiepileptics needed an increase in the dose of drugs for seizure control as compared to the first generation group, although not statistically significant. This probably could be due to better potency and seizure control of the first generation AED, but this better control of seizure activity with first generation AED medications comes with greater risk of major congenital malformations, putting both the neurologist and the obstetricians in a state of constant debate as to what would be the preferred drug for such females.

Conclusion

To conclude, we would like to emphasize that almost one quarter of people affected with epilepsy are women of reproductive age group.²³ The risks to the fetus associated with drug exposure needs to be weighed against the risk of maternal disease. There is a place for preconceptional counseling for all women with epilepsy. Optimizing the dose of AED, preferring monotherapy in the lowest possible dose, avoiding valproate as far as possible, informing about the teratogenicity and folate supplementation, all form a part of the preconceptional conversation.

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None.

Conflicts of interest

The authors declare there is no conflict of interests.

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