Section: Neurology

Original Research Article

THE IMPACT OF EPILEPSY ON THE MATERNAL AND FOETAL OUTCOME

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Abstract

Background: The ultimate goal is safe and happy motherhood with minimal or no harm to the foetus. Antiepiletic drug intake prenatally or during pregnancy is associated with congenital malformations which can be major or minor. **Material & Methods:** Women with Epilepsy (WWE) in the reproductive age group who were planning pregnancy or became pregnant were included in the study and were followed up throughout the course of pregnancy, and 3 months postpartum. Patients with first episode of seizure during pregnancy, seizures due to complications from diabetes or hypertension, or started on anti-epileptic drugs after the first trimester were excluded. **Results:** Pregnancy Outcome: 87 % had an uneventful course throughout their pregnancy and delivered at term. 9% had preterm delivery. 80% had a normal vaginal delivery at term. 4% had a difficult labour and delivered by forceps. 3 had abortion. 4 % developed postpartum haemorrhage and another 4% post-partum seizures. Foetal Outcome: Congenital Malformations (CM) occurred in 6% of primigravida and 1% of multigravida. 72% out of 100 patients were on monotherapy with 42% on phenytoin (PHT), 23% on carbamazepine (CBZ) and 7% on sodium valproate (SVP). The incidence of congenital malformations was 3 in those on phenytoin, 1 in carbamazepine. **Conclusion:** It is important to educate pregnant women with epilepsy for proper planning of their pregnancies, for preconceptional folic acid intake, AED intake during the course of pregnancy, and also monitor with high resolution ultrasound for the detection of congenital malformations. Since congenital malformations are higher with polytherapy, proper prepregnancy epileptic drug change and optimizing their dosages are essential for a successful outcome.

INTRODUCTION

Epilepsy is the commonest neurological disorder in clinical practice. There are approximately 2.73 million women affected by epilepsy in India and about 52% of them are in the reproductive age group. Epilepsy can occur in women during any part of their life time, either at puberty, pregnancy or menopause.

Aim of The Study

To study the alteration in the frequency of seizures during pregnancy, the outcome of pregnancy and delivery. To study the effect of epilepsy and anti-epileptic drugs on the foetus and neonate. To compare and analyse the outcome of pregnancy in patients with or without pre-conceptional counselling.

MATERIALS AND METHODS

Women with Epilepsy (WWE) in the reproductive age group who were planning pregnancy or became pregnant were included in the study. Patients with epilepsy attending epilepsy clinic at Institute of Neurology, Madras Medical College, Chennai and also Regional Institute of Obstertics and Gynaecology Government Hospital (RIOGH), Egmore who were on antiepileptic drugs before and during pregnancy were enrolled. All patients were followed up throughout the course of pregnancy, and 3 months postpartum.

Exclusion Criteria

Patients with first episode of seizure during pregnancy, seizures due to complications from

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diabetes or hypertension, or started on anti-epileptic drugs after the first trimester were excluded.

Methods /Analysis

Demographic profile of patients were recorded. Detailed history regarding the age of onset of epilepsy, duration, seizure type, frequency of seizures, dosage of AEDS, number of drugs were obtained. Detailed neurological examination was performed. EEG, and Magnetic Resonance Imaging of the Brain was obtained. Women and their families were educated about the pregnancy outcomes. Nutritional status (obese and underweight women), other intercurrent illness, diabetes, hypertension, urinary tract infection were assessed. Risk reduction were started prior to conception in all WWE.

The following maternal characteristics were analysed.

Seizure type during pregnancy was classified according to International league against epilepsy. The change in seizure frequency during pregnancy, number of antiepileptic drugs and their respective minimum and maximum dosages were noted.

If the patient was on monotherapy or polytherapy. If the patient was treated with polytherapy various drug complications were analyzed (phenytoin+ carbamazepine), (phenytoin + carbamzepine+ sodium valporate), (sodium valporate+ carbamzepine), (sodium valporate+ phenytoin+ levetiracetam).

Correlation of drug dosage with foetal outcome.

The dosage of individual drugs required was analysed. Patient was maintained on the lowest and effective dosage to control seizures.

All patients were encouraged to take folic acid 5mg prior to conception regularly. Women with epilepsy who were in the reproductive age group were counselled to take folic acid in the pre-conception period regularly.

Obstetric data obtained from their antenatal records., which included gestational age at booking, preconceptal folic acid intake, Hypermesis gravidarum, pre-eclampsia. Abruptio placentae, premature labor were watched for carefully in women as they predispose to poor drug compliance and seizure control.

Screening for foetal characters in the first, second and third trimester. To watch for neural tube defects. Alpha foetal protein assay was done as and when required. In the second trimester targeted anomaly scan was done and looked for major defects which include cardiac defects, and urogenital defects. In the third trimester IUGR, foetal biophysical profile were assessed.

Mode of Delivery

Pregnancy outcome assessed the spontaneous loss before 20 weeks of gestation, still births. Premature delivery was defined as delivery before gestational week 37, and prolonged pregnancy as lasting longer than 42 weeks.

Whether the patient underwent induced or spontaneous labour, instrumentation during labour, elective or emergency caesarian section noted. Types of anaesthesia and their mode of administration were looked for.

Seizure outcome in the postnatal period

Patients in the postnatal period were monitored for increased stress of the postnatal period and sleep deprivation and motivated for regular drug intake.

Foetal Outcome

Apgar score at 1 minute, 5minutes, birth weight, head circumference, major and minor congenital anomalies, specific drug related abnormalities were assessed. Vitamin K was given for all babies after delivery. Small-for-gestational-age newborns are defined when the weight is below the tenth percentile when adjusted for gestational age and sex for the normal population. Infants with birth weight <2,500 g were considered to have low birth weight. Major malformations were defined as structural abnormalities with surgical, medical, or cosmetic importance and were identified by the paediatrician, who examined the infants at birth and at discharge from the hospital.

To provide adequate breast feeding and neonatal care and to monitor for feeding difficulties.

RESULTS

Demographic Profile

Maternal age: The mean age of the cohort was 25 years, with maximum age of 39 years.

PARITY:Among 100 patients examined, 52% were primigravida , 48% multigravida.

Educational Status: On viewing their educational status, 30% of them were found to be illiterate , 54% attained primary education , 11% secondary education , only 5% graduated from college.

Working Status: Most of them were home markers constituting about 92% ,8% of them were working women.

Causes for Seizures

Among 100 patients about 47 of them had previous history of CVT, active granuloma, calcified lesions , benign tumours and 53 of them were idiopathic . 99 had a normal neurological examination , one had a left hemiparesis with hemiatrophy . 53 had a normal imaging either by CT or MRI and 47 had abnormality on neuroimaging . The EEG was normal in 42 , abnormal in 58.

pre-conceptional Folic Acid Intake

Folic acid was taken by most of them pre-conceptionally amounting to 96% . 4% of them never consumed folic acid prior to pregnancy.

COMPLICATIONS:

One women developed GDM during her pregnancy course , 2 of them developed pregnancy induced hypertension . 70 % of the pregnant women with epilepsy were suffering from anaemia . Hyperemesis gravidarum occurred more frequently in these women , which made it difficult to take oral medications for them. Figure 1.

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Maternal Seizure Profile and Antiepiletic Drug Intake

On viewing their epileptic diary it was found that 81% had generalized tonic clonic seizures, 12 % complex partial seizures, 2% simple partial seizures with secondary generalization, 5% complex partial seizures with secondary generalization. Figure 2.

Antepartum Seizure Frequency

83 of 100 patients had good seizure control prior to pregnancy.10 of these 83 had increased seizures during pregnancy.17 of those 100 who had poor seizure control prior to pregnancy also noted an increase in seizure frequency during pregnancy. 1% had staus epilepticus . Age of onset of epilepsy , duration , and etiology had no relationship to seizure occurrence. Figure 3.

Anti-Epileptic Drugs (AEDs)

Number of drugs: Out of 100 patients 72% was on monotherapy, 20% on two drug regime, 8% on polytherapy. Figure 4,5. The dose of AEDs RANGED FROM 200 - 400mg for phenytoin, 400-600mg on sodium valproate, 400-1200mg for carbamazepine.

Change of Drug

About 21% had a change in drug dosage during their pregnancy and 79% maintained their pre-pregnancy drug dosage.Ultrasound evaluation done under high resolution during their first trimester did not reveal any abnormality in any of them. 2 had neural tube defects during their third trimester. 5 of them were diagnosed with congenital malformations after delivery.

Pregnancy Outcome

Duration of Delivery

87 % had an uneventful course throughout their pregnancy and delivered at term. 9% had preterm delivery. 80% had a normal vaginal delivery at term. 4% had a difficult labour and delivered by forceps., 3 had abortion. One of them had still birth and all of them had good seizure control during pregnancy. 6% emergency LSCS and 6% elective LSCS because of foetal distress.The indication was obstetric with failed induction, foetal distress, a big baby. 4 % developed postpartum haemorrhage and another 4% post-partum seizures. Figure 6.

Foetal Outcome

5 had an APGAR SCORE of less than 5 at 1 minute which improved to 7 or more at 5 minutes. 25% had low birth weight of below 2.5kg, 75% had a normal birth weight between 2.5 to 3.5kg.

Congenital Malformations (CM) occurred in 6% of primigravida and 1% of multigravida. 72% out of 100 patients were on monotherapy with 42% on phenytoin (PHT), 23% on carbamazepine (CBZ) and 7% on sodium valproate (SVP). The incidence of congenital malformations was 3 in those on phenytoin, 1 in carbamazepine.Figure 7.

20 out of 100 patients were on two drug regimens. In SVP + CBZ combination CM occurred in 1 and one in PHT+SVP. Among 8 of them on polytherapy one had malformation.The relationship between drug regimen and congenital malformation is 5.6% (4 of 72) on monotherapy, 10.0% (2 out of 20) on two drug regimen,12.5% (1of 8) on polytherapy. Figure 8. Among those who presented with malformations, 4 had generalised tonic clonic seizures, one had complex partial seizures, one had simple partial seizure with secondary generalisation, one had complex partial with secondary generalization. All of them had preconceptional folic acid intake and had no contributory risk factors including gestational diabetes, preeclampsia, eclampsia.

Children with CM were delivered through spontaneous vaginal delivery. 6 of the neonates with congenital malformations delivered at term and 1 at preterm. The major congenital malformations observed were 1 dermoid cyst, 3 neural tube defects, 1 Arnold chiari formation, meningocoele, meningomyelocoele, spina bifida. 2 with cardiac defects ventricular septal defect, atrial septal defect. These were detected upto 1 month after delivery.

All the neonates hd a good apgar score at 1 and 5 minutes despite their malformations. But feeding difficulties were encountered in 2 neonates with cardiac malformations. 1 baby had NICU admission.

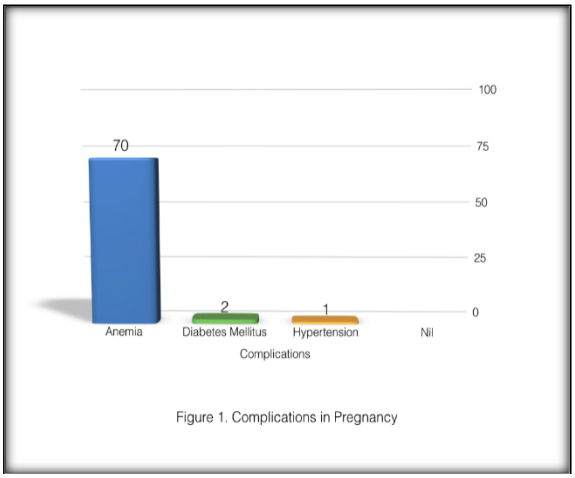

Figure 1. Complications in Pregnancy

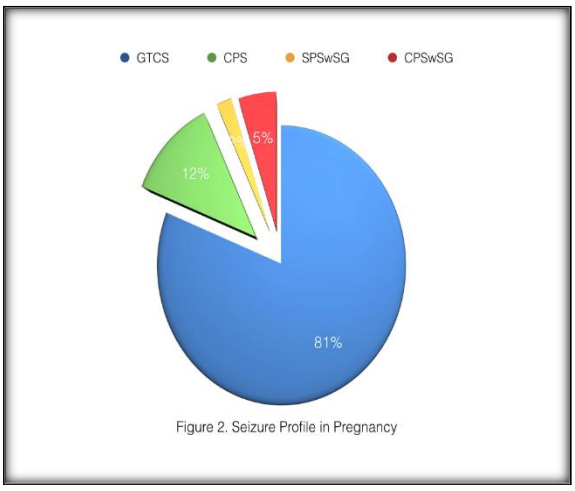

Figure 2. Seizure Profile in Pregnancy

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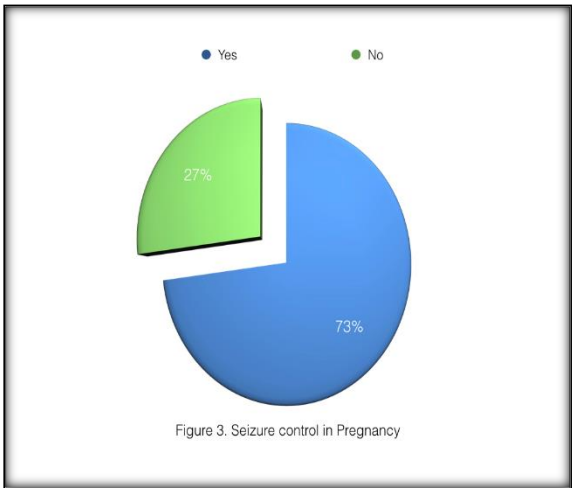


Figure 3. Seizure control in Pregnancy

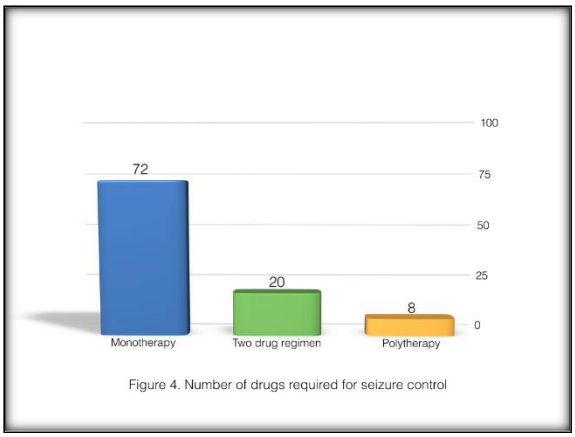


Figure 4. Number of drugs required for seizure control

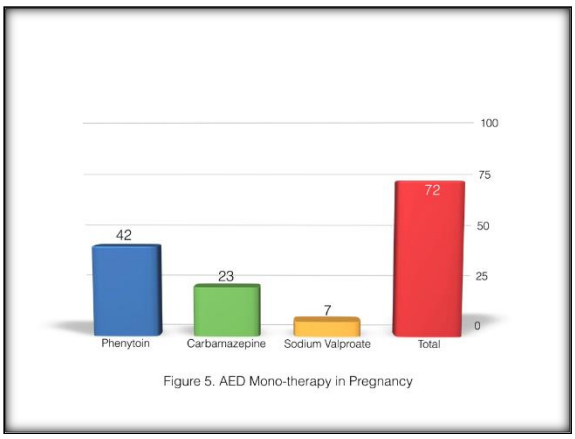


Figure 5. AED Mono-therapy in Pregnancy

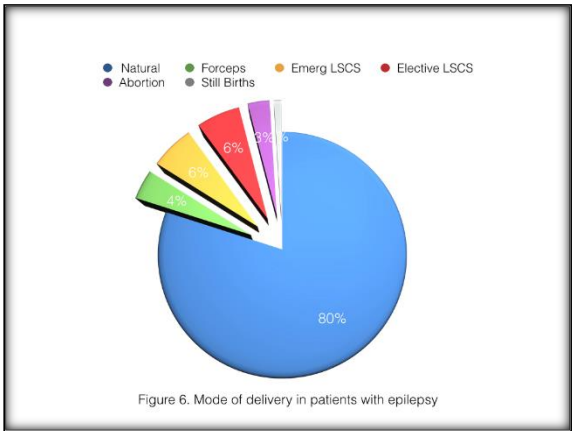
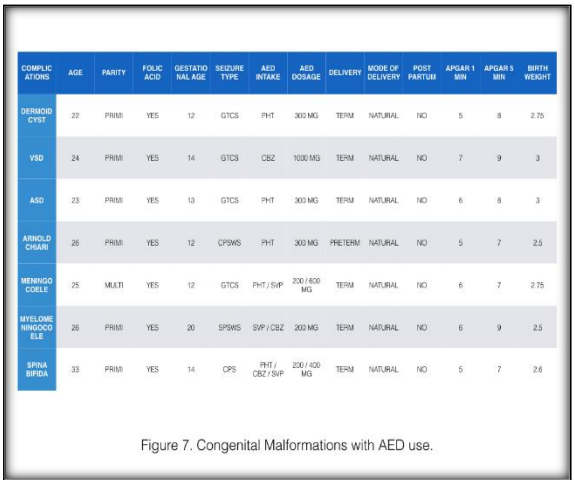


Figure 6. Mode of delivery in patients with epilepsy



COMPLICATIONS	AGE	PARITY	FOLIC ACID	GESTATIONAL AGE	SEIZURE TYPE	AED INTAKE	AED DOSAGE	DELIVERY	MODE OF DELIVERY	POST PARTUM	APGAR 1 MIN	APGAR 5 MIN	BIRTH WEIGHT
DERMOID CYST	22	PRIMI	YES	12	GTCS	PHT	300 MG	TERM	NATURAL	NO	5	8	2.75
VSD	24	PRIMI	YES	14	GTCS	CBZ	1000 MG	TERM	NATURAL	NO	7	9	3
ASD	23	PRIMI	YES	13	GTCS	PHT	300 MG	TERM	NATURAL	NO	6	8	3
ARNOLD CHIARI	26	PRIMI	YES	12	CPSWS	PHT	300 MG	PRETERM	NATURAL	NO	5	7	2.5
MENINGOCOELE	25	MULTI	YES	12	GTCS	PHT / SVP	200 / 600 MG	TERM	NATURAL	NO	6	7	2.75
MYELOMENINGOCOELE	26	PRIMI	YES	20	SPSWS	SVP / CBZ	200 MG	TERM	NATURAL	NO	6	9	2.5
SPINA BIFIDA	33	PRIMI	YES	14	CPS	PHT / CBZ / SVP	200 / 400 MG	TERM	NATURAL	NO	5	7	2.6

Figure 7. Congenital Malformations with AED use.

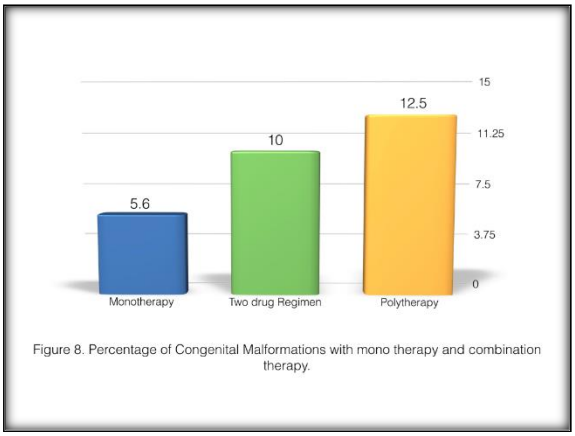


Figure 8. Percentage of Congenital Malformations with mono therapy and combination therapy.

DISCUSSION

Women with epilepsy usually fear that the risk of pregnancy complications and birth defects would be higher because her baby will be exposed to antiepileptic drugs. However, many women with epilepsy and their treating physicians believe these risks to be higher than they really seemed to be.

Our study was mainly done in WWE who took AEDs prior to and during pregnancy. Consanguineous parentage was excluded from our study to minimise the role of genetic factors on the foetal outcome.

According to Richmond et al.[21] there was a increased risk of PIH [<0.5] in WWE. The rate of preeclampsia was not significantly increased in a prospective study of 179 pregnancies of WWE with regards to singleton pregnancy at Finland. In A Swedish study by Christina philo et al.[22] done on 1207 women taking AEDs in pregnancy found a significant increase in the incidence of pre-eclampsia (OR 1.66, 95% - CI 1, 43-1.89). There was no increased risk of preeclampsia or GDM in our study population.

The EURAP registry on 1882 WWE recorded seizure freedom in 58% of participants during pregnancy. When first trimester seizure activity was used a reference, 64% had no change in the second and third trimester, 16% improved, while only 17% deteriorated. The Australian Register by Vajda et

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al.[11] found that an year of seizure freedom prior to conception reduced the pregnancy risks of having seizures by 50-70%. But in our study 27% had an increase in their seizure frequency in the antepartum period and one among them developed status epilepticus. In 17 of them it was either because of poor drug compliance, fear of intake of antiepileptic drugs causing congenital malformations in the child, not able to procure drugs because of their shift of residence. Some of them developed seizures despite good drug compliance. 73% had no increase in seizure frequency. There was no relationship between the seizure duration and frequency of seizures. The increase in frequency occurred both in generalised and partial epilepsy groups.

Walker et al .[35] reported that women with good seizure control (e.g. seizure free for 2-5 years) may be eligible to stop or reduce their medication prior to pregnancy, and women taking more than one AED may be considered a trial of monotherapy, if they have normal neurological examination/IQ, EEG and neuroimaging, as the risk of getting a seizure is much lower. In our study 27% had change in medication to monotherapy because of good seizure control. All of them had a normal neurological examination and EEG.

Pregnant women with Epilepsy have a higher induction rate. This has been reported with two previous studies in which 33% and 19% were induced, but contrary to the finding in a study from Japan where no difference was seen. According to guidelines in Norway and England, epilepsy is not an indication for induction in uncomplicated pregnancies. The induction rate was low in our women 4 of them were induced and delivered by forceps and most of them had spontaneous vaginal delivery. 12% of 100 patients were delivered by caesarian section, 6 by elective, 6 by emergency LSCS due obstetrical causes.

An increase in vaginal bleeding during late pregnancy and delivery, has been reported with previous studies (Pennell; Pilo et al).[13,22] but in our study group 4 patients developed PPH. Alterations in vitamin K metabolism may also be a causal factor (Crawford; Pilo et al,) .[22] possibly associated with use of enzyme-inducing AEDs.

EURAP registry data regarding the impact of seizures on pregnancy outcome in 1956 WWE, had a stillbirth rate of (1.5%) which is higher than in the general population of 0.5% Earlier reports have suggested higher mortality in infants born to mothers with epilepsy; [Hiilesmaa et al.; Meador et al.[24]due to poor control of maternal seizure. There was 1 abortion, 3 still births in our study. No neonatal deaths were seen.

Foetal Outcome

Low birth weight and low apgar score was seen in epileptic mothers exposed to AEDs in the literature.[33,37] In our study low birth was seen in 25% of the mothers exposed to AEDs. 5 of 100 neonates had an apgar score of less than 5 at 1minute which improved to 7 or more at 5 minutes, leading to favourable birth outcomes in our study group.

The U.K. registry.[31] reported a higher malformation rate with VPA, 5.9% (4.3-8.2%; 95% CI), than with CBZ (2.3% [1.4-3.7%]) or LTG (2.1% [1.0-4.0%]). The types of congenital malformations found in pregnancies exposed to monotherapy with either carbamazepine, valporate, and phenytoin were similar to those previously reported abnormalities. An American Academy of Neurology Practice Parameter.[19] concluded the increased the risk for major congenital malformations associated with AED intake during the first trimester and with polytherapy.

The incidence of malformations for monotherapy for carbamazepine was 4.6%, lamotrigine was 2.9%, phenobarbitol was 4.9%, phenytoin was 7.4% and valporate was 10.7%, with VPA having a higher dosage related relation either as monotherapy or polytherapy.[11,26,38] The rate of congenital malformations is 2 to 3% in the general population, reported rates in offspring of women with epilepsy ranges from 1.25 to 11.5%, with the combined yielding a rate of 4 to 6%. Previous studies by reports reported an increase in congenital malformations [31,38, 39]. In our study 7 of 100 WWE delivered a child with congenital malformations. In monotherapy group it was 7.142% (3 of 42) on therapy with phenytoin, 4.34% (1 of 23) on carbamazepine. On 2 drug regimen it was 1 with SVP+PHT, 1 with CBZ+SVP. In polytherapy group it was 12.5%(1 of 8). CM risk is 5.6% on monotherapy, 10.0% on two drug regimen, 12.5% on polytherapy.

The congenital malformations in our group were Neural tube defects (NTDs), cardiac malformations, dermoid cyst. The relative risk of malformation was higher with monotherapy and polytherapy in our pregnant women with epilepsy. Studies have shown that folic acid is effective in reducing malformations in the general population, but not in AED-exposed pregnancies. Studies have revealed an association between CBZ exposure in utero and NTDs. NTDs occur in 6/10,000 pregnancies. Lingh et al has associated spina bifida aperta as the specific NTD associated with VPA & CBZ exposure.[55]

Neural tube defects, can be prevented if folic acid is initiated pre-conceptionally, and every effort must be taken to improve folic acid supplementation in women with epilepsy, and majority of our patients were on preconceptional folic acid including those with congenital malformations. In our study, preconceptional folic acid supplementation was higher in AED-treated pregnancies, especially when treated with valproate or polytherapy.

A prospective multicenter, observational study revealed that fetal exposure to valproate resulted in significantly lower IQ at age 3 compared to carbamazepine, lamotrigine or phenytoin. The effect of valproate on lowering fetal IQ was dose dependent. In our study the dose of valproate was

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significantly reduced without affecting the seizure frequency.[24]

CONCLUSION

1. Most of our pregnant patients had good seizure control before and during pregnancy.
2. In those with poor seizures control prior to pregnancy had improved seizures during pregnancy, due to stringent monitoring and care.
3. Status epilepticus occurred in one patient.
4. Most of our patients had successful vaginal delivery. In those who had caesarian section it was done for non-neurological indication like cephalo-pelvic disproportion, foetal distress.
5. During postpartum period only one of them developed seizures.

The incidence of congenital malformations, CM risk is 5.6% on monotherapy, 10.0% on two drug regimen, 12.5% on polytherapy. There were no neonatal deaths.

It is important to educate pregnant women with epilepsy for proper planning of their pregnancies, for preconceptional folic acid intake, AED intake during the course of pregnancy, and also monitor with high resolution ultrasound for the detection of congenital malformations.

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