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Observational Study of Obstetric and Neonatal Outcome of Pregnancy in Women with Epilepsy

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ABSTRACT

Aims: To determine the obstetric and neonatal outcome of pregnancy in women with epilepsy

Materials and methods: This is an observational study conducted in was conducted in the Department of Obstetrics and Gynaecology in total number of 200 patients were studied out of which 50 pregnant women with epilepsy were taken as cases and 150 randomly selected pregnant women were taken as controls. The obstetric and neonatal outcome of pregnancy was compared in cases and controls. In cases, the seizure frequency in pregnancy, interval of last seizure before pregnancy and the AED used are compared.

Results: According to the present study, maximum numbers of patients were in the age group 20-30 years in both the groups. The occurrence of oligohydramnios was 14% in cases and 12% in controls. IUGR was seen in 10% in cases and 12% in controls. The occurrence of preterm deliveries is 14% in cases and 4% in controls. The percentage of IUD was 6% in cases and 14% in controls. The rate of antepartum haemorrhage was 4% in cases, while it was 3.33% in controls. The subsequent development of preeclampsia was 12% in cases and 15% in controls. Mode of delivery was through the caesarean section in 47.92%, vaginal delivery in 52.08% and outlet forceps in 2.08% of the cases. In controls 20% delivered by LSCS, 74.67% had the vaginal delivery and 4.17% were delivered by outlet forceps. Induction of labour was done in 12.50% of cases and 12% of controls. The babies with birth weight <2.5kg was 31.37% in cases and 46% in controls. NICU admissions have been three for babies of women with epilepsy. Congenital anomalies in the newborn are seen in three cases on AED. In this study in cases on AED, seizures occurred during pregnancy in 16.66%cases and there were no seizures during pregnancy in 83.44% cases. In cases not on AED, seizures occurred in 45% cases, there were no seizures in 55% cases. In 15 (50%) cases Levetiracetam was used. In 2 (6.66%) cases carbamazepine was used. In 8 (26.68%) cases phenytoin was used. Combination of phenytoin and clobazam were used in 3 cases and Levetiracetam and clobazam were used in 2 cases. One maternal death in cases was found in the present study.

Conclusion: Diagnosis of epilepsy still implies a slightly increased risk of adverse pregnancy, delivery, and perinatal outcomes.

Keywords: Epilepsy, Adverse pregnancy, Delivery, Perinatal outcomes.

INTRODUCTION

Epilepsy is a neurological disorder marked by sudden recurrent episodes of sensory disturbance, loss of consciousness, or convulsions, associated with abnormal electrical activity in the brain. Women with epilepsy are believed to be at an increased risk during pregnancy. Complication rates vary among patients. A slightly increased risk of complications and obstetric outcomes like antepartum haemorrhage, caesarean section, foetal distress, low birth weight babies, intrauterine foetal death, and congenital malformations are found in pregnancies of women with the known case of epilepsy.

Epilepsy is one of the common chronic conditions affecting women of reproductive age. The rates of maternal death are ten-fold higher in women with epilepsy than those without the condition. Care of women with epilepsy continues to be fragmented, with few units providing joint obstetric-epilepsy care. The Confidential Enquiries into Maternal and Child Health in the UK highlighted that epilepsy was not always perceived as a high-risk condition in pregnancy. Adequate engagement with women diagnosed to have epilepsy is needed during pre- conception and pregnancy to plan appropriate management.[1, 2]

Quantification of the risks associated with pregnancy in women with epilepsy is essential for appropriate counselling and provision of care. The current evidence tends to be focussed on foetal harm from in – utero anti-epileptic drug (AED) exposure, or on the severity of maternal seizures, with less emphasis on other pregnancy outcomes. Individual studies

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provide varied and imprecise estimates of the association between epilepsy and pregnancy complications such as abortion, preterm delivery, antepartum and post-partum haemorrhage, caesarean section, foetal growth restriction and admission to neonatal intensive care unit.[3]

Women with epilepsy (WWE), who are considering pregnancy, may have concerns about worsening of seizures, obstetric complications, abnormal delivery and malformations in their children. Previous research has shown that most WWE experience no increase in seizures during pregnancy. Several authors have found an increased prevalence of specific complications including vaginal bleeding, anaemia, vomiting, hypertension and breech presentation. Others concluded that most WWE has uncomplicated pregnancies. Increased caesarean section rate, pre-term delivery, low birth weight, increased rates of nonproteinuric hypertension (P<.05), induction of labour

(P<.001), and foetal cardiovascular malformations (P<.001) among women with epilepsy have been reported.[4] There is a 12-13 fold increase in major congenital malformations (MCM) in babies of WWE treated with a single antiepileptic drug (AED) during pregnancy. Higher rates have been reported with sodium valproate. A review of several studies found increased stillbirth and neonatal death in pregnancy with epilepsy but this was not replicated in two studies. Increased maternal mortality during and soon after pregnancy is also recognized.[5,6] This observational study is an attempt to look into pregnancy outcomes of patients with epilepsy who reported to Gandhi medical college when compared to randomly selected patients without epilepsy.

PATIENTS AND METHODS

This is an observational study conducted in the Department of Obstetrics and Gynaecology, Gandhi Medical College, Secunderabad between October 2015 and September 2017. The study included a target number of 200 subjects with 50 as cases and 150 as controls.

The cases comprised of 50 women with epilepsy complicating pregnancy fulfilling the inclusion and exclusion criteria. Controls comprised of 150 pregnant women fulfilling the inclusion criteria and exclusion criteria selected randomly. All the women gave informed consent to participate in the study, which was approved by the institutional ethics committee.

Inclusion Criteria : Pregnant women with epilepsy attending the antenatal clinic at Gandhi medical college between 2015-2017.

Exclusion Criteria: Pregnant women with other conditions like 1. Diabetes Mellitus, Renal Disorders, Liver Disorders, Heart Diseases, Thyroid, Maternal Infections and Autoimmune Disorders 8. Eclampsia
Maternal and fetal complications are recorded abortions/ Still Birth, Oligohydramnios, Intrauterine Growth Restriction, Preterm Labor, Low Birth Weight, Intrauterine Fetal Death, Antepartum Hemorrhage, Seizures In Pregnancy, Development of pre eclampsia and Maternal Death
Fetal complications like Intrauterine Growth Restriction(IUGR), Intrauterine Foetal Death, Apgar Score At 5 Minutes, Birth Weight, Congenital Anomalies, NICU Admissions and Neonatal Deaths (If Any)

Statistical Analysis:

The values are presented as the mean ± standard deviation. The statistical tool applied was by using the Open Epi, Version 3. Qualitative and quantitative data were analyzed by chi-square. The results were considered statistically significant when the probability of the null hypothesis was less than 5% ($p<0.05$). The mean commonly known as the average, is the sum of n observations or measurements divided by n and it is given by Where x is called variable and n stands for a number of observations. The most popular and frequently used measure of variability is the standard deviation (SD). The standard deviation is defined as "square-root of the mean of the squares of all the deviations being measured from the mean of the observations". It is given by

For n < 30 samples and when the sample size is more than 30 (n > 30), the SD is calculated by Chi-squared test

$$Mean = \bar{x} = \frac{\sum_{i=1}^{n} x}{n}, \quad SD = \sqrt{\frac{\sum (x - \bar{x})^2}{n-1}}, \quad SD = \sqrt{\frac{\sum \left(X - \bar{X}\right)^2}{n}}$$

chi-squared testis any statistical hypothesis test wherein the sampling distribution of the test statistic is a chi-squared distribution when the null hypothesis is true. The chi-squared test is used to determine whether there is a significant difference between the expected frequencies and the observed frequencies in one or more categories.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 09, 2023

RESULTS

Table-1: Distribution in cases and controls by status of fetal coplications

Age groups	**Cases**	**%**	**Controls**	**%**	**Total**
<=20yrs	10	20	25	16.67	35
21-30yrs	37	74	112	74.67	149
>=31yrs	3	6	13	8.67	16
Mean age	24	-	24.60	-	-
SD age	4	-	3.60	-	-
B/U/C					
B/C	25	50	67	44.67	92
U/C	25	50	83	55.33	108
Total	50	100.00	150	100.00	200
Chi-square =0.429 P = 0.5123					
Gravida					
PrimiGravida	18	36	52	34.67	70
Multi Gravida	32	64	98	65.33	130
Total	50	100.00	150	100.00	200
Chi-square = 0.029 P = 0.8641					
Gestational age					
<28 weeks	3	6	6	4.00	9
28-32 weeks	1	2	3	2.00	4
32-37weeks	4	8	3	2.00	7
Term	42	84	138	92.00	180
Total	50	100.00	150	100.00	200
Chi-square =4.4571, p value 0.2161					
Previous h/o					
Abortions, IUD	4	8	11	7.33	15
Live	46	92	139	92.67	185
Total	50	100.00	150	100.00	200
Chi-square = 0.024 P = 0.8768					
Oligohydramnios					
Yes	7	14	18	12.00	25
No	43	86	132	88.00	175
Total	50	100.00	150	100.00	200
Chi-square = 0.137 P = 0.7111					
Abortions					
Aborted	2	4	6	4.00	8
Total	50		150		200

The maximum numbers of cases were between 21 to 30 years and the mean age is 24.2 years in cases and 24.60 years in control. The numbers of booked cases were 50% in cases and 44.67% in controls. Women who belonged to primigravida were 36% in cases and 34.67% in controls. The numbers of multigravida women were 64% in cases and 65.33% in controls. This table shows the distribution of cases and controls according to gestational age, term pregnancies were 84% in cases and 92% in controls. The occurrence of abortions/IUD in previous pregnancy was 8% in cases and 7.33% in controls. The occurrence of oligohydramnios was 14% in cases and 12% in controls, which was not statistically significant. The percentage of abortions in cases was 4% and in controls it was 4%. The difference is not significant statistically.

Table-2: Comparison of cases and controls by status of foetal complications

IUGR	**Cases**	**%**	**Controls**	**%**	**Total**
Yes	5	10	18	12.00	23
No	45	90	132	88.00	177
Total	50	100.00	150	100.00	200

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 09, 2023

Chi-square = 0.147 P = 0.7010					
Preterm delivery					
Yes	7	14	6	4.00	13
No	43	86	144	96.00	187
Total	50	100.00	150	100.0	200
Chi-square = 6.170 P = 0.0130*					
IUD					
Yes	3	6	21	14.00	24
No	47	94	129	86.00	176
Total	50	100.00	150	100.00	200
Chi-square = 2.273 P = 0.1317					
APH					
Yes	2	4	5	3.33	7
No	48	96	145	96.67	193
Total	50	100.00	150	100.00	200
Chi-square with Yates's correction = 0.049 ,P=0.8242					
Preeclampsia					
Yes	6	12	15	10.00	21
No	44	88	135	90.00	179
Total	50	100.00	150	100.00	200
Chi-square = 0.16 P = 0.6895					

*p<0.05

The occurrence of IUGR was 10% in cases and 12% in controls, which is not statistically significant. There were 14% of preterm deliveries in cases, while it was 4% in controls. This showed that the difference is statistically significant. The percentage of IUD was 6% in cases and 14% in controls, the difference is not statistically significant. The percentage of antepartum haemorrhage in cases was 4%, while it was 3.33% in controls. The difference is not significant statistically.
The subsequent development of preeclampsia was 12% in cases and 10% in controls and the result is not statistically significant.

Table-3: Comparison of cases and controls with mode of delivery

Mode of delivery	**Cases**	**%**	**Controls**	**%**	**p-value**
LSCS	23	47.92	32	20.00	0.0006*
EL LSCS	6	12.50	5	2.00	0.0198*
EM LSCS	17	35.42	27	18.00	0.0279*
TOTAL VD	25	52.08	112	74.67	0.0015*
INDUCED VD	6	12.50	18	12.00	0.500
SPONTANEOUS VD	16	33.33	94	62.00	0.0001*
UNAIDED SPVD	15	31.25	88	58.67	0.0003*
OUTLET FORCEPS	1	2.08	6	4.17	0.5048
TOTAL	48	100.00	144	100.00	
Chi-square=34.613 P = 0.00001322*					

The delivery by LSCS was 47.92% in cases and 20% in controls and difference is statistically significant.

Table -4 : Comparison of cases and controls by status of birthweight

Birth weight	Cases	%	Controls	%	Total
<2kg	5	10	12	8.00	17
2-2.5kg	11	22	57	38.00	68
>2.5kg	32	64	75	50.00	107
Abortions	2	4	6	4.00	8
Total	50	100.00	150	100.00	200
Chi-square =4.3738 P = 0.2238					

The babies with birth weight <2.5kg was 32% in cases and 46% in controls. The difference is not significant statistically.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 09, 2023

Table-5 – intragroup comparison of seizure frequency in pregnancy in test group

Seizures in pregnancy	**Women using Antiepileptic drug**	**%**	**Women Not using antiepileptic drug**	**%**
Yes	5	16.66	9	45
No	25	83.4	11	55
Total	30	100	20	100
Chi-square =4.778 P = 0.0288*				
Interval of last seizure before pregnancy				
<5 years	21	70	6	30
>5 years	9	30	14	70
Folic acid use				
Yes	30	100	20	100
No	0	0	0	0

Occurrence of seizures in pregnancy in the cases was 16.66% in those using AEDs and 45% in those not on AEDs

Table-6: Intragroup comparison of type of drug used in women using antiepileptic drugs

Drug	No of cases	% of cases
Carbamazepine	2	6.66
Levetiracetam	15	50
Levetiracetam, clobazam	2	6.66
Phenytoin	8	26.68
Phenytoin, clobazam	3	10

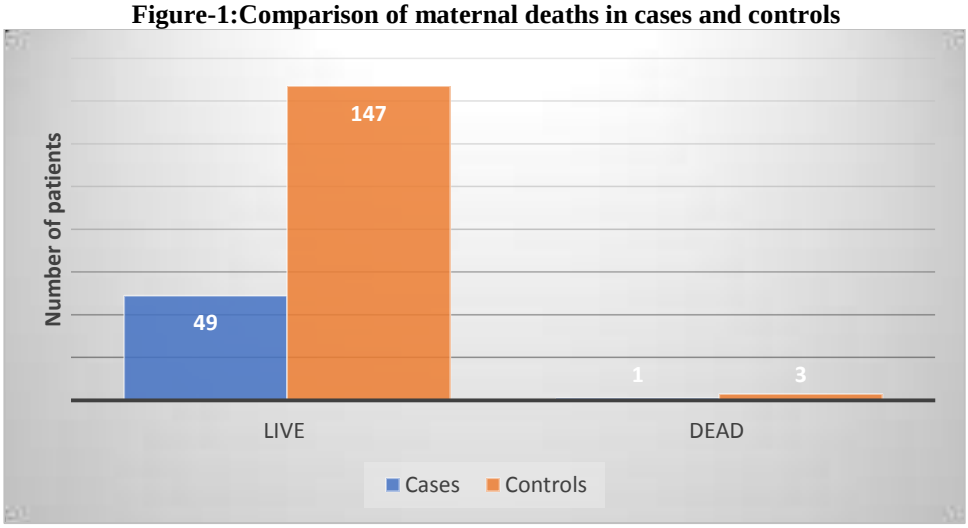
The AED used was carbamazepine in 6.66%, levetiracetam in 50%, phenytoin in 26.68%, the combination of levetiracetam and clobazam were used in 6.66%, phenytoin and clobazam were used in 10% cases.

Table -7: Intragroup comparison of birth weight of baby in cases

Birth Weight	Not on antiepileptic drugs	%	On antiepileptic drugs	%
<2 kgs	1	5.26	4	13.79
2-2.5kgs	4	21.05	7	24.14
>2.5kgs	14	73.68	18	62.07
Chi-square =1.0818 P = 0.5822				
Neonatal Outcome				
NICU	1	5.26	2	6.90
Congenital anomalies	0	0	3	10.34

5 babies born to women, not on AED are below 2.5 kg and 11 babies born to women on AED are below 2.5 kg weight. There is no statistical significance in this comparison There were 3 babies born with congenital anomalies in those on AEDs. The NICU admissions were 3 of 45 live births in cases, all were discharged healthy . NICU admissions were 9 of 123 live births in controls, all were discharged healthy.

Figure-1:Comparison of maternal deaths in cases and controls



There was 1 maternal death in 50 cases and 3 maternal deaths in 150 controls. This result is not statistically significant.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 09, 2023

DISCUSSION

Epilepsy is a neurological disorder in pregnant women, with an incidence rate of 0.3–0.7%. Despite its rarity, epilepsy can cause different clinical problems during pregnancy and the rate of maternal mortality is ten times higher in women with epilepsy compared with those without epilepsy. Thus, growing interests focus on exploring maternal complications and pregnancy outcomes. [7]

Epilepsy requires medical treatment in pregnant women. Therefore, more and more scholars focused on exploring the effects of AED. The earliest use of AED therapy dates back to 1850. The present goal of epilepsy treatment is freedom from seizures without significant adverse effects. However, once epileptic women become pregnant, continuing AED treatment may pose concerns. Thus, at the time of initiating AED treatment, epilepsy control and foetus development must be balanced. therefore; important considerations for epileptic women include planning for pregnancy, prenatal counselling, and management of delivery. [8,9,] Women with epilepsy possess small but significantly increased rate of adverse pregnancy outcomes. This observational study focuses on pregnancy outcome in women with epilepsy. This study also focused on pregnancy outcome of women with epilepsy using various anti-epileptic drugs.

Distribution of age of samples randomly selected as tests and controls showed that the mean age of cases is 24.20 and of controls is 24.60.In the samples selected for this study, maximum cases and controls have fallen into the age group of 21-30 years. This is in accordance with various studies that stated that the common childbearing age is between 21-30 years. Mean age of pregnant women with epilepsy is slightly lower than women without epilepsy in this study. This is in accordance with the systematic review and meta-analysis done by Neda razaz *et al.* [10] which stated that the mean age of women with epilepsy at the time of delivery is less than mean age of women without epilepsy.

Comparison of the number of cases in the sample that have been registered, and are being followed up, with the number of unbooked cases in both test and control groups showed that the numbers of booked cases in test and control groups are 50% and 44.67% respectively. Comparatively high numbers of unbooked cases were present in this study as Gandhi medical college is a tertiary centre and most of the unbooked cases were those referred from peripheral hospitals for a multidisciplinary management and better care of the pregnant woman.

Comparison of the number of primigravida and multigravida in cases and controls is done. The number of primigravida and multigravida are 36% and 64% respectively in cases and 34.67% and 65.33% respectively in controls. This data is in accordance with the systematic review done by Neda razaz *et al.* [10] who stated that a major number of cases and controls are of multiparity. Comparison of the gestational age showed that majority of the patients delivered at term (37-40 weeks). The number of term gestation was 84% in cases and 92% in controls. Majority of the cases proceeded till term gestation without any major complications. This is in accordance with the review done by Neda razaz *et al* [10] on the association between pregnancy and perinatal outcomes among women with epilepsy, which states that most of the cases proceeded until term gestation.

Comparison of the previous obstetric history regarding abortions and IUD in cases and controls is done. With regard to the fetal loss in previous pregnancies, the rate of IUD/abortions is 8% in cases and 7.33% in controls.

Complication of oligohydramnios in cases and controls is studied. Oligohweramnios is defined as an amniotic fluid index ≤5 cm or single deepest pocket of amniotic fluid ≤2 cm. In this study, oligohydramnios was seen in 14% of cases and 12% of controls. The result showed no statistically significant difference between cases and controls. In a study conducted by Chawla L *et al.* [11] , the percentage of oligohydramnios in cases was 5% and controls were 3.4% which was not statistically significant, which is in accordance with the present study.

Comparison of IUGR in cases and controls is done in the present study. Intrauterine growth restriction (IUGR), a condition that occurs due to various reasons, is an important cause of foetal and neonatal morbidity and mortality. It has been defined as a rate of foetal growth that is less than normal in light of the growth potential of that specific infant. Usually, IUGR and small for gestational age (SGA) are used interchangeably in literature, even though minute differences exist between them. SGA has been defined as having the birth weight less than two standard deviations below the mean or less than the 10th percentile of a population-specific birth weight for specific gestational age. [12]

These infants have many acute neonatal problems that include perinatal asphyxia, hypothermia, hypoglycaemia, and polycythaemia. The likely long-term complications that are prone to develop when IUGR infants grow up includes growth retardation, major and subtle neurodevelopmental handicaps, and developmental origin of health and disease.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 09, 2023

Hence in this study comparison of IUGR between control group and test group is done. This study showed no statistically significant difference in the rate of IUGR in cases (10%) and controls (12%).

In a study conducted by Chawla L *et al*.[11] the rate of IUGR in cases was 13.5% and in controls was 9.4% which was not statistically significant, similar to the present study. In a study by Anette Huuse *et al*.[13] the effects of epilepsy and AED exposure were significant in IUGR. CBZ was the most frequently used AED, and the only AED that was significantly associated with smaller babies. The clinical importance of these findings is to be studied further with larger sample size.

Victoria M. Kelly[14] studied Obstetric outcomes in women with multiple sclerosis and epilepsy and the most concerning findings in this group were higher rates of IUGR (OR 1.9), and antenatal hospitalization, with a rate almost 3 times higher than controls (OR 3.0).Previous studies of pregnancy outcomes in epilepsy have primarily evolved from AED registries that examined rates of congenital malformations according to medication exposure. The studies regarding maternal outcomes have had varied results.

A recent prospective study of 650 women with epilepsy in India by Thomas SV[15] found no significant increase in HTN, caesarean delivery, or low birth weight. This study evaluated women throughout pregnancy and did report higher rates of spontaneous abortion, which occurred mostly outside the hospital. A smaller study from Finland by Viinikrainen K *et al*[16] found higher rates of IUGR in women with active epilepsy.

Some studies of specific AEDs have reported increased rates of IUGR, especially among women who were treated with multiple AEDs. Anette Huuse Farmen[13] studied Intrauterine growth retardation in foetuses of women with epilepsy and stated that the weight of placenta was slightly lower in the epilepsy group than in the controls. Reduced placental weight may indicate placental dysfunction, which may lead to reduced growth of the foetus. A previous study reported a tendency towards smaller birth weight in children of mothers with epilepsy not using AED while the frequencies of placental disorders were not increased.

However, low BMI before pregnancy may predispose to small placental weight and, thus, smaller infants. There was a significantly higher risk of the ponderal index being below the 10th percentile and infants being small for gestational age (SGA) in the epilepsy group; exposure to AED increased the risk, and in the AED group, the frequency of SGA and the low ponderal index was highest in Lamotrigine exposed women. In the AED group, head circumference was significantly smaller among Carbamazepine exposed women.[13] contradicting evidence suggests that further studies with large sample size will give deeper insights into IUGR in pregnant women with epilepsy.

Comparison of the rate of preterm labour in cases and controls is studied. World health organization defines preterm delivery as babies born alive before 37 weeks of pregnancy are completed. There are sub-categories of preterm birth, based on gestational age: extremely preterm (less than 28 weeks), very preterm (28 to 32 weeks), moderate to late preterm (32 to 37 weeks).

In this study, Preterm labour was seen 14% of cases and 4% of controls, which was statistically significant. In a population-based study by Ingrid Borthen *et al*[17], an increased risk of preterm birth before 34 weeks of gestation in women with epilepsy using AEDs, OR: 1.6 (1.2–2.1) was seen. In a hospital-based study, by Ingrid Borthen *et al*[3] both cases with epilepsy with and without AED use had an increased risk of preterm birth before 32 weeks of gestation. These studies are in accordance with the present study. Sarah McDonald *et al*[18] did an observational study on Mortality and Morbidity during Delivery Hospitalization among Pregnant Women with Epilepsy in the United States and stated that women with epilepsy were also more likely than women without epilepsy to experience preeclampsia, preterm labour, haemorrhage, and chorioamnionitis.

An evidence-based review done by "Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society" concluded that it is probable that WWE taking AEDs do not have a moderately increased risk of premature contractions and premature labour and delivery during pregnancy and it is possible that WWE who smoke do have a substantially increased risk of premature contractions and premature labor and delivery during pregnancy compared to women without epilepsy who smoke.

Viinikainen *et al*.[19] in their study showed no substantially increased risk of premature contractions or premature labor and delivery in WWE taking AEDs compared to control women without epilepsy (OR 0.51, 95% CI 0.19 –1.36).

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 09, 2023

Hvas CL *et al.*[20] showed an increased risk for WWE who were smokers compared to control women who were also smokers (OR 3.4, 95% CI1.8 – 6.5) (data not given for all WWE compared to controls)for premature labour. Mawer G *et al*[21] concluded that there were no significant differences in the frequencies of pre-term deliveries in epileptics and non epileptics.

Comparison of the rate of IUD in cases and controls showed the rate of IUD as 6% in cases and 14% in controls in this study, which is not statistically significant. Intrauterine foetal death is foetal death occurring beyond the period of viability during pregnancy or during labour. In a study conducted by Raji C *et al*[22] Intrauterine foetal death (IUFD) occurred in 8.57% cases and the result was not statistically significantly similar to the present study. Tomson *et al.*[10] reported Antiepileptic Drugs and Intrauterine Death: A Prospective Observational Study From EURAP and concluded that the most important risk factors for intrauterine death in pregnancies of women with epilepsy include maternal exposure to AED polytherapy and the presence of MCMs in at least one of the parents. Women were enrolled in EURAP up to 16 weeks of gestation with a median gestational age at enrolment of 8 weeks. From a study of spontaneous miscarriage, most miscarriages occurred prior to 12 weeks gestation with a peak at 7 weeks . In a large dataset of 4,539 women, which included women enrolled prior to conception, the overall rate of spontaneous miscarriage was 13%. We can probably assume, therefore, that the EURAP study slightly underestimates the overall spontaneous miscarriage rates by missing early pregnancies and underestimates stillbirth rates by not including those that occurred later in pregnancy. The authors found that unmodifiable risk factors, such as a history of previous miscarriage and maternal age, were risk factors for intrauterine death, as reported in the general population. The unique risk of intrauterine death in the epilepsy subpopulation with a family history of MCM is intriguing. Further understanding of AED effects on placental functioning may also be important when unravelling the risks of pregnancies in women with epilepsy.

In a systematic review and Meta-analysis done by Razaz *et al.*[10] the frequency of stillbirth was higher in offspring of women with epilepsy compared with those without epilepsy (0.6% vs. 0.3%). After adjustment for potential confounders, neonates of women with epilepsy had significantly higher risks of stillbirth, being born 52 SGA, both medically indicated and spontaneous preterm births, major congenital malformations, neonatal infections, asphyxia-related complications, low 5-minute APGAR scores, and neonatal hypoglycaemia and respiratory distress compared with neonates of unaffected women.

Comparison of the rate of antepartum haemorrhage in cases and controls showed the rate of antepartum haemorrhage to be 4% in cases and 3.33% in controls in the present study .The difference was not significant statistically. Study by Viinikrainen K *et al.*[16] also supported the above result, which is in accordance with the present study.

Borthen *et al.*[3] observed that women with epilepsy and AED use had an AED-induced folate deficiency and alteration in the metabolism of vitamin K- dependent blood clotting factors as the cause of vaginal bleeding in late pregnancy. A five-fold increased risk of early vaginal bleeding among women with epilepsy using AEDs was also seen. The differences may be due to patient selection and small sample sizes in the hospital-based studies while the study by Borthen is a national cohort study.

According to a systematic review by Razaz *et al.*[10] there was no increased risk of antepartum and postpartum haemorrhage in pregnancies of women with epilepsy compared with those without epilepsy; however, this association was of borderline significance (aRR, 1.61).The results of systematic reviews by Razaz *et al* are similar to the results of this study. A large sample might give further insight into the occurrence of antepartum haemorrhage in women with epilepsy in Indian population.

Comparison of the rate of preeclampsia in cases and controls showed that the rate of preeclampsia in cases was 12% and in controls was 10%. The result was not significant statistically. Preeclampsia in pregnancy is characterized by new onset hypertension after 20 weeks and proteinuria. Preeclampsia is the most common complication of pregnancy. It affects about 5% of pregnancies. It occurs in the third trimester (the last third) of pregnancy.

Goel *et al.*[23] conducted a study in which the rate of preeclampsia in cases was 24.3% and controls were 15.4% and the difference was not statistically significant. This is in accordance with the present study. Harden *et al.*[9] in an evidence-based review for American Academy of Neurology and American Epilepsy Society concluded that there is insufficient

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evidence to support or refute an increased risk of preeclampsia in WWE taking AEDs. Borthen *et al*[3] in their hospital-based study observed that women with epilepsy and AED use had an increased risk of severe preeclampsia and early vaginal bleeding, OR: 5.0 (1.3–19.9) and OR: 6.4 (2.7–15.2), respectively. These data were adjusted for maternal education, smoking, body mass index, medical conditions, and diabetes.

The increased risk of preeclampsia was related to using of Lamotrigine monotherapy in pregnancy. This effect of Lamotrigine in pregnancy is similar to what has previously been reported for carbamazepine. Borthen *et al*[3] also observed that both active epilepsy and no active epilepsy had an increased risk of severe preeclampsia, respectively. This increased risk was only observed in AED users.

Comparison of the abortion rate in controls and cases showed that 4% of women with epilepsy and 4% of controls had abortions. These findings are not statistically significant. The observations of this study are contradictory to the finding of Harden *et al*[9] that preterm labour, spontaneous abortions are common in pregnant women with epilepsy. Comparison of the mode of delivery in cases and controls is studied in the present study. Vaginal delivery was seen in 25(52.08%) of the cases and 112(74.67%) of controls. This difference is significant statistically. Induction of labour was done for 6(12.5%) of cases and 18(12%) of controls. The difference was not significant statistically. Forceps application was seen in 1(2.08%) of the cases and 6(4.17%) of controls. The difference was not significant statistically. In the present study 23 women (47.92%) delivered by caesarean section in cases and 32women (20%) of controls. All caesareans were performed for obstetrical indications like foetal bradycardia, Meconium stained liquor, contracted pelvis, previous caesarean section, failed induction and breech presentation. There was a statistically significant difference in the rates of caesarean delivery between cases and controls. The difference is due to obstetrical causes. In a study conducted by Ozdemir *et al*.[24] 22 (14.76%) women had normal spontaneous vaginal, and 118 (79.20%) had the caesarean delivery. The causes for caesarean section were neurologist's recommendation due to frequent seizures during pregnancy in 33.05%, history of caesarean delivery in 38.13%, unstable heartbeat trace in 27.12%, and malpresentation in 1.7% of the patients.

In another study by Chawla *et al*.[11] Vaginal delivery was seen in 36(61%) of the mothers. Forceps application was seen in 2(3%) of the patients. 21(36%) delivered by caesarean section. All caesareans were performed for obstetrical indications. 10(48%) caesareans were done for feta bradycardia, 3(14%) on patients request, 2(9%) for Meconium stained liquor and contracted pelvis each and 1(5%) each for the arrest of cervical dilatation, failed induction, breech presentation, and eclampsia. In the control group, 42 patients (18%) delivered by caesarean section, but this difference in the rates of caesarean section was not significant (p=0.44). These results indicate that epilepsy in pregnancy is not an indication for caesarean delivery. Luz Viale *et al*.[25] conducted a systematic review on Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis and concluded that their meta-analysis has provided precise quantitative estimates of the magnitude of the association between epilepsy in pregnancy, exposure to antiepileptic drugs, and various maternal and foetal outcomes. In pregnant women, a diagnosis of epilepsy is associated with a small but significant increase in adverse pregnancy outcomes such as antepartum and post-partum haemorrhage, spontaneous miscarriage, hypertensive disorders, induction of labour, caesarean section, any preterm birth, and foetal growth restriction

The findings of the review and meta-analysis are in accordance with the observation of this study wherein there were increased caesarean sections in women with epilepsy Comparison between the birth weights in cases and controls is done. Low birth weight (LBW) is defined by the World Health Organization as a birth weight of an infant of 2,499 g or less, regardless of gestational age. Normal weight at term delivery is 2500–4200 grams.
The birth weight <2kg was 10% in cases and 8% controls. The birth weight 2-2.5 kg was 22% in cases and 38% controls. The birth weight >2.5kg was 64% in cases and 50% in controls. The difference in birth weights was not significant statistically. More than 60% of babies in cases weighed >2.5 kg.

Latika Chawla *et al*.[11] in their study found that 26(44%) of the new-born 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. This is comparable to the present study as in both the studies most of the babies weighed >2 kg.

Intragroup comparison of seizure frequency in pregnancy in epileptics, between cases on treatment and cases not on treatment is studied. In this study in cases on AED, seizures occurred during pregnancy in five (16.66%) cases and there were no seizures during pregnancy in 26 (83.34%) cases. In cases not on AED, seizures occurred in nine (45%) cases, there were no seizures in 11 (55%) cases. This difference is significant statistically. In the total cases 72% remained seizure free during pregnancy. There was 1 case in which the patient was not on AED, she was a known case of epilepsy since 1 year, stopped medication without advice and was admitted with status epilepticus, she was primi gravida with 16 weeks gestation, aborted spontaneously, came with aspiration pneumonitis. She was intubated, started on AED, but her

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condition deteriorated and she expired after 2 days. throughout pregnancy, which is comparable to the present study. Although the majority of women remain seizure-free throughout pregnancy, this data suggests that a more proactive approach to adjusting the dose of all AEDs in pregnancy should be considered, in particular for those pregnancies with seizures occurring in the first 72 % of cases remained "unchanged" while 8 and 19 % respectively "improved" and "worsened"; moreover, there was no statistical difference in the number of seizure-free patients and in the monthly seizure frequencies. No differences were found in controls. This prospective study concluded that pregnancy does not affect seizure frequency in women with epilepsy

In the present study of 30 cases on AED in 21 cases (70%) the last seizure before pregnancy was <5 years, in 9 cases(30%) the last seizure before pregnancy was >5 years. In cases not on AED during pregnancy, in 6(30%) the last seizure before pregnancy was <5 years and in 14(70%) the last seizure before pregnancy was >5 years. Folic acid was used by all cases (100%).

Nature of antiepileptic drug and the combination therapy of antiepileptic drugs have an influence on pregnancy outcomes. In the observation of this study, women on antiepileptic drug usage are using monotherapy of levetiracetam/carbamazepine / phenytoin and women on combination therapy are using phenytoin+clobazam or levitiracetem+clobazam. In 15(50%) cases Levetiracetam was used. In 2(6.66%) cases carbamazepine was used. In 8 (26.68%) cases phenytoin was used. Combination drugs were used in 5 cases.

Levetiracetam with clobazam was used in 2 (6.66%) cases. Phenytoin with clobazam was used in 3 (10%) cases. In women on Levetiracetam 6 (37.5%) had the seizure during pregnancy and no cases of congenital anomalies are found. In cases on Phenytoin 4(50%) had seizures in pregnancy and 2(25%) cases had congenital anomalies in newborn. In the present study, Levetiracetam is the most used drug.

effective than the older AEDs in keeping pregnant women with the major types of epilepsy seizure-free. They also claimed that the drug has little or no teratogenic potential, with a major congenital malformation rate of 0.7% in monotherapy in 304 pregnancies and it does not seem to have deleterious effects on subsequent intellectual development in childhood. Therefore, there are grounds for considering it among the agents of the first choice in women contemplating pregnancy, and to be suitable for use in most circumstances in women who have the potential for pregnancy, unless the type of seizure disorder present, or other consideration, make that Levetiracetam is the preferable drug in pregnancy. In this study, there are no reported congenital malformations in neonates of women using levetiracetam.

with levetiracetam monotherapy use in pregnancy. MCM risk is higher when levetiracetam is taken as part of a polytherapy regimen, although further work is required to determine the risks of particular combinations. With respect to MCM, levetiracetam taken in monotherapy can be considered a safer alternative to valproate for women with epilepsy of childbearing age. This is also in accordance with the present study wherein there were congenital anomalies in two cases of phenytoin monotherapy but none with levetiracetam.

The comparison of birth weights of babies in cases on AED and not on AED is done. In cases on AED 4(13.79%) had birth weight <2kgs, 7(24.14%) had birth weight 2-2.5kgs and 18(62.07%) had birth weight >2.5kgs. In cases not on AED,1 (5.26%) had birth weight <2kgs, 4(21.05%) had birth weight 2-2.5kgs and 14(73.68%) had birth weight >2.5kgs. More than 50% of the babies were >2.5kgs. The difference in birth weights was not statistically significant in the present study. In the present study the number of NICU admissions in cases was 3(6.66%) and in controls was 9(7.31%). According to the present study, there is no increased risk of NICU admissions in cases when compared to controls. This is in contradiction to study done by Artama *et al.*[26] In cases Artama *et al*[26] found a clearly increased risk of respiratory care and admission to neonatal intensive care unit in offspring of WWE. In a systematic review done by Nadem razaz[10] women with epilepsy were more likely than women without epilepsy to have an infant who experienced asphyxia-related neonatal complications, neonatal hypoglycaemia, and neonatal respiratory distress. In another meta-analysis done by Allotey *et al.*[25], admission to Neonatal Intensive Care Unit (NICU) was found to be 12.5 per 100 pregnancies. The reasons for infants admitted to NICU is varied and with changing practice, advancement in medical care and higher detection rates of outcomes such as foetal growth restriction and preterm birth may explain the high prevalence rates in these findings. The variations in maternal and offspring outcomes in pregnant women with epilepsy should be considered when counselling women with epilepsy. It is essential that 60 women with epilepsy should have discussions with their health care provider prior to conception, with the focus on the importance of a planned pregnancy and careful management to minimise their risks of adverse maternal or fetal outcomes.

In the present study, there were 3(10%) cases in which the newborn had congenital malformations in cases on AED. In cases of phenytoin, there was 1 baby with cleft lip and 1 baby with cleft lip and polycystic kidney disease. In cases on

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carbamazepine, there was one baby with prominent cisterna magna. There were no anomalies in cases on levetiracetam. phenytoin (PHT) were at an increased risk of malformation compared with children born to women without epilepsy and to women with untreated epilepsy. Children exposed to carbamazepine (CBZ) were at a higher risk of malformation than children born to women without epilepsy and women with untreated epilepsy. There was no increased risk for major malformation for Lamotrigine (LTG) and levetiracetam (LEV). Based on the evidence, LEV and LTG exposure carried the lowest risk of overall malformation. This is in accordance with the present study that the risk of congenital malformations is less with newer AED like levetiracetam. However further studies are to be done in this aspect.

The rate of maternal deaths in cases and controls is studied. There was 1(1.96%) maternal death in cases, in which the case was a primigravida with 16 weeks gestation, known case of epilepsy since 1 year, not on treatment, the patient came with status epilepticus, aborted spontaneously, aspirated during the convulsion, had a cardiac arrest. In controls, there was 3(2%) maternal death. The difference was not statistically significant.

MacDonald *et al*.[5] conducted a study in which the frequency of death at delivery hospitalization was 80 deaths per 1,00,000 pregnancies for women with epilepsy and 6 deaths per 1,00,000 pregnancies for women without epilepsy. This corresponded to a more than 10-fold increased risk of death for women with epilepsy compared with women without epilepsy. Part of the increased risk may be mediated by the higher prevalence of potentially life-threatening obstetrical complications such as preeclampsia and postpartum haemorrhage.

Alternatively, the deaths may have occurred because of complications directly related to seizures; for example, the patient may have gone into status epilepticus or experienced aspiration of fluids during a seizure. The rate of sudden unexpected death among persons with epilepsy has been reported to be nearly 24 times that of the expected rate among the general population, and thus sudden unexpected death could be a possible explanation for the increased risk. Regardless of the specific cause, the point that women recorded as having epilepsy have an increased risk of mortality remains a clinically relevant message suggesting that increased attention should be paid. Future research is needed to determine the specific causes of mortality and how interventions might improve outcomes the mortality of pregnant women with epilepsy.

CONCLUSION

The present study provides reassurance to women with epilepsy that, epilepsy in pregnancy in the majority of women is uneventful. AED use during pregnancy is generally not associated with adverse maternal and foetal or neonatal outcomes, although it is important to be aware that AEDs differ in their teratogenic potential. However, a diagnosis of epilepsy still implies a slightly increased risk of adverse pregnancy, delivery, and perinatal outcomes. This information should improve counselling for women with epilepsy who contemplate discontinuing their treatment during pregnancy and provide useful information to their health care clinicians.

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