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Profile and Outcome of Newborns Born to Mothers with Epilepsy: A Pediatrician's Perspective

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ABSTRACT

Epilepsy complicates approximately 0.6 per 100 of all pregnancies. Epilepsy in pregnancy has a bearing on pregnancy course and neonatal outcomes. Indian studies in this regard are sparse, old and moreover were undertaken mostly by obstetricians. The present study was planned looking from a pediatrician's perspective in order to study all possible neonatal outcomes born to mothers with epilepsy delivered by any mode. The data consisted of retrospective (old patient records with obstetric and neurological details including EEG and MRI reports) and prospective data (monitored from the rst antenatal visit to the delivery regularly by obstetricians and neurologists) conducted in a tertiary care government medical college hospital. Pregnant women with Epilepsy on Anti Epileptic Drugs AED and their newborns born by caesarean section were enrolled from 2017- 2020. These women were treated according to their epilepsy type, focal and generalized and was followed for certain events (outcome) from delivery till discharge. These outcomes were compared between the test groups (mothers with >1 AED, not well controlled epilepsy and associated comorbidities) and the control groups (mothers with 1 AED, well controlled epilepsy and no associated comorbidities). Statistical Analysis SPSS vs 17 software used for statistical analysis. Descriptive analysis, Chi Square test and multiple logistic regression were used. Statistical level of significance was xed at $p<0.05$. 55 pregnant women with epilepsy and their 55 newborns were seen. Neonatal outcome was adverse in 58% babies., 47% were born to mothers with comorbidities. 25 newborns (45%) had low birth weight, 15 (27%) were preterm, 20 (36%) had jaundice. 18 (33%) were small for gestational age, 8 babies (15%) had congenital anomalies (cardiac-7., non cardiac-3). There were 2 neonatal deaths (4%). Statistically signi cant outcome was found with respect to prematurity in those with >1 AED group and also was significant with respect to prematurity, Low Birth Weight LBW, Intrauterine Growth Retardation IUGR in those with co morbidities. The outcome of newborns is in uenced by the controlledness of epilepsy in mothers, number of AED used and those mothers with comorbidities.

OPEN ACCESS

Key Words

Co-morbidities, epilepsy, AED, prematurity, malformations, congenital anomaly, levetiracetam

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INTRODUCTION

Epilepsy complicates approximately 0.6 per 100 of all pregnancies[1,2]. Proper planning of pregnancy and switching over to safer alternative Anti Epileptic Drugs (AED) is crucial to improve both the maternal and neonatal outcomes[1,2]. The outcome in the present era is much brighter compared to earlier decades because of the advent of newer and safer AEDs[1-3]. 2nd generation AEDs like Levetiracetam, Lamotrigine, Topiramate are safer alternatives to 1st generation ones like valproate, phenobarbitone, phenytoin, carbamazepine[1-5]. Adverse neonatal outcomes occur because of mostly use of AED rather than epilepsy itself. Prolonged epilepsy can cause intrauterine hypoxia, preterm labour, IUGR, perinatal depression in baby but inappropriate AEDs can additionally cause major malformations and bad perinatal events[5-7]. Indian studies looking into this aspect are far and few and moreover almost all studies have been undertaken by the west and by obstetricians. The present study was conducted at a referral tertiary care.

MATERIALS AND METHODS

The present study is a descriptive study consisting of retrospective and prospective data. It was conducted in a tertiary care Government medical college hospital called Bowring hospital then attached to Bangalore Medical College Research Institute, Bangalore Karnataka, India . The inclusion criteria consisted of pregnant women with Epilepsy enrolled at same hospital in Bangalore from 2017 to 2020 and their newborns who were all born by any mode of delivery. This medical college hospital is equipped with proper obstetric and neonatal back up and proper neurology department to see the mothers . Owing to the same reason, the study population is a heterogeneous one with cases comprising of mothers with >1 or 1 AED, well or not so well controlled epilepsy, pregnant women with other comorbidities. Hence, in this study of outcomes of newborns born to mothers with epilepsy, we have attempted to look at a paediatrician's perspective rather than an obstetrician's view. Those with Pregnancy Induced Hypertension , poorly controlled epilepsy >=1/week, severe intellectual disability were not included. The study received institutional ethics committee approval. Informed consent was obtained from patients before data collection. Investigations done as per hospital protocol. The retrospective study design consisted of old patient records with obstetric and neurological details including EEG and MRI reports. Prospectively each pregnant woman was monitored from the rst antenatal visit to the delivery regularly by obstetricians and neurologists. It was mainly a cross sectional study of neonates after birth. All mothers were on AED, either 1 or more depending on the control of epilepsy and choice of AED depended on type of epilepsy like focal or generalized .

The following baseline characteristics were noted in all pregnant women: age, parity, weight, antenatal booking status, bad obstetric history (BOH), type of epilepsy, control of epilepsy, presence of fits during present pregnancy, presence or absence of other comorbidities like psychiatric migraine, intellectual disability and tests including EEG , MRI brain ndings of mother (fetal echocardiography was done for those whose anomaly scan showed cardiac defect), status at pregnancy, use of AED medications >=1 and dosage used , AED changed in course of pregnancy , Folic acid used preconceptionally or in pregnancy and its dosage , complications during pregnancy, presence of obstetric risk factors like pregnancy induced hypertension, premature rupture of membranes, malpositions, hypothyroidism, oligohydramnios etc., The neonatal events were observed in the form of APGAR scores, birth weight using CDC charts, gestational age using New Ballard scoring, neonatal deaths, co-morbidities like jaundice, respiratory distress, metabolic disturbances, feed intolerance, seizures, sepsis, polycythemia, congenital anomalies including CHD, dysmorphism, for which fetal echocardiography was done, requirement of CPAP/ventilator etc. Adverse neonatal events were Low Birth Weight (Extremely Low Birth Weight and Very Low Birth Weight included), Prematurity, Small for Gestational Age, Large for Gestational Age, Neonatal Deaths, Co-morbidities like Jaundice, Congenital Anomalies, CHDs, Respiratory Distress, etc. These neonatal outcomes were compared between groups of newborns born to mothers with and without comorbid factors, born to mothers with >1/1 AED , born to mothers with well controlled and not so well controlled epilepsy. SPSS v 17 software was used for statistical analysis. Descriptive analysis was used to summarize baseline characteristics of the study population using mean and standard deviation for continuous variables and proportion and percentage for ordinal variables. Chi Square test of proportion was used to assess the statistical significance of difference in proportions between the dependent neonatal outcomes and independent maternal risk factors. Multiple logistic regression was used to assess the relation between neonatal outcomes and maternal factors. Statistical level of significance was xed at $p<0.05$.

RESULTS AND DISCUSSIONS

Maternal Parameters: Out of total 20000 babies screened, the study population consisted of 55 pregnant women with Epilepsy and their 55 newborns (singleton pregnancies) born by any mode of delivery

Table 1: Description of Co-Morbidities

Description of Co-Morbidities	Preterm AGA	Preterm SGA
Central Nervous System CNS	sensorium	2 (4)
	Seizures Intra cranial bleed	3 (5)
	sensorium	1 (2)
Respiratory	RDS TTNB	3 (5)
System RS	Pneumonia	1 (2)
Cardio Vascular	RDS TTNB	1 (2)
	Hypotension	3 (5)
System CVS		
	Tachycardia	4 (7)
	CHD	7 (13)
Gastro Intestinal System GIT	Feed intolerance	4 (7)
	NEC	1 (2)
Renal Eye	ARF	1
	Cataract	1
	ROP	1
Hematological	Anemia	1
	Polycythemia	3
	Thrombopenia	3
	Leukocytosis	5
	Leukopenia	1
	Jaundice	20 (36)
Metabolic	Hypoglycemia	7 (13)
	Hypocalcemia	5 (9)
	Hypomagnesaemia	2 (4)
	Metabolic acidosis	5 (9)
Immunological	Sepsis	3 (5)
Temperature	Hypothermia	4 (7)
	Hyperthermia	0
Congenital anomalies	Cardiac	7 (13)
	Non Cardiac	3 (5)

Table 2: Distribution of Congenital Anomalies Including CHD

Congenital anomalies (n=8) including CHDs Cardiac (n = 7)	type of anomaly in baby	AED used in mother	Number of cases (n = 8)
	ASD and dysmorphism	LAM+LEVE	1 (2)
	ASD	TOPIRAMATE	1 (2)
	PDA TGA	TGA LEVETIRACETAM	1 (2)
	VSD dysmorphism	LEVE + TOPI	1 (2)
	PDA with ASD	LEVETIRACETAM	1 (2)
	CoA with ASD	TOPIRAMATE 1 (2)	1 (2)
Non Cardiac (n=3)	meningocele	VALPROATE	1 (2)
	Ambiguous Genitalia cleft palate	PHENO + LEVE	1 (2)
	Talipes equinovarus	LEVETIRACETA M	1 (2)

Table 3: Major Neonatal Outcomes

	Number of Cases in Not well Controlled Epilepsy	Number of Cases in well Controlled epilepsy	P-value
	(n=24)	(n=31)	
prematurity	11 (46)	4 (13)	0.01
LBW	11 (46)	14 (45)	0.58
IUGR	7 (29)	11 (35)	0.77
Jaundice	9 (38)	11 (35)	0.43
Congenital Anomalies including CHD	5 (21)	3 (10)	0.24
CHD	5 (21)	2 (6)	0.22
Neonatal Death	2 (8)	0	0.18
Maternal Death	2 (8)	0	0.07

Table 4: Neonatal and Maternal Outcomes in Mothers with >1 AED VS on 1 AED

Major Outcomes	Number of cases in >1 AED (n=27)	Number of cases in 1 AED (n=28)	P-value
prematurity	10 (37)	5 (18)	0.09
LBW	12 (44)	13 (46)	0.54
IUGR	7 (26)	11 (39)	0.22
Jaundice	8 (30)	12 (43)	0.35
Congenital anomalies including CHD	3 (11)	5 (18)	0.37
CHD	2 (7)	5 (18)	0.22
Neonatal Death	1 (4)	1 (4)	1.0
Maternal Death	1 (4)	1 (4)	0.48

Table 5: Major Outcomes

	Number of Cases in those born with other comorbidities	Number of case with no Comorbidities	P-value
	N=18	(n=37)	
Prematurity	10 (56)	5 (14)	0.003
LBW	14 (78)	11 (30)	0.001
IUGR	11 (61)	7 (19)	0.003
Jaundice	10 (56)	10 (27)	0.06
Congenital anomalies including CHD	5 (28)	3 (8)	0.06
CHD	4 (22)	3 (8)	0.14
Neonatal Death	1 (6)	1 (3)	0.61
Maternal Death	1 (6)	1 (3)	0.03

Among the 55 newborns, M:F=25:30. 1 child had a birth weight <1kg., 2 had birth weight between 1.0-1.49kg., 4 were in 1.5-1.99kg group., 18 in 2.0-2.49 kg group and 30 weighed =2.5kg at birth. 40 were born at term and 15 were preterm. Based on the gestational age, 40 were in 37-42 weeks range., 12 in 34-36 weeks., 2 in 31-33 weeks and 1 was in 28-30 weeks group.

Neonatal Parameters: Out of 55 babies, about 15 male babies (47%) and 17 female babies (53%) had adverse outcomes. Maximum events were LBW (25/45%) followed by jaundice in 20/36, IUGR in 18/33, prematurity in 15/27, congenital anomalies including CHD in 8/15, CHD in 7/13 and neonatal death in 2/4. 25 babies (45%) had low birth weight out of which 1 was Extremely Low Birth Weight (ELBW) and 2 were Very Low Birth Weight (VLBW). 18 had intrauterine growth retardation (IUGR) (33%) of which 7 were preterm and 11 were term. 15 had prematurity (27%) of which 7 were small for gestational age (SGA) and 8 were appropriate for gestational age (AGA). Among the term babies, 11 were SGA and 29 were AGA. None were large for gestational age. So the maximum outcomes were term AGA (29 or 52%) followed by term SGA (11 or 20%) preterm AGA (8 or 15%) and preterm SGA (7 or 13%). About 20 (36%) babies had jaundice, 8 (15%) had congenital anomalies including CHD, 7 (13%) had only CHDs and 13 (24%) had other co-morbidities as listed in **(Table 1)**. 6 babies (11%) had poor APGAR scores requiring active resuscitation all in the form of bag and mask ventilation. 2 babies were depressed neurologically due to the effect of maternal general anaesthesia. These babies had APGAR scores of 4-6 requiring active resuscitation in the form of bag and mask ventilation but then quickly recovered. None required chest compressions or drugs. Of these 3 (5%) required mechanical ventilation. Two babies died within the neonatal period (4%) due to extreme prematurity 27 weeks and <1kg ELBW. 8 babies had congenital anomalies including CHD in 7 **(Table 2)**.

2 babies had both cardiac and non cardiac anomalies. Out of these 4 mothers were on 2 AED, 3 babies had non cardiac anomalies like meningocele in mother on valproate, ambiguous genitalia on mom with Phenobarbitone and levetiracetam, talipes on mother with levetiracetam. None were on preconceptional folate but all were on folate 5mg/d after pregnancy was confirmed. The one with meningocele had started folate at 2 mo pregnancy . Among the 55 women with epilepsy, 24 (44%) had well controlled epilepsy (<=1/month or never in pregnancy and the remaining 31 (56%) had >1/month but <=3/month and around 20 had 1-3 seizures in present pregnancy too, no status epilepticus. Around 40 had epilepsy >10 years and remaining <10 years. Well controlled epilepsy subgroup (24) had focal seizures only and some of whom were on Carbamezepine/valproate pre pregnancy were switched over to various other AEDs. 1 lady on valproate arrived in labour directly, hence her AED was not changed outside too. 20 had generalized epilepsy only and 11 had both focal and generalized epilepsy. All had EEG before. About 20 had epileptiform discharges. Rest were normal. Around 20 had underwent MRI before and were normal in 18. 2 had calcified Neurocysticercosis. None were on preconceptional folic acid . None had bad obstetric history like abortions or baby with malformations. All were on regular folic acid 5mg/day as soon as pregnancy was confirmed in 1st trimester. Around 45 were on Levetiracetam,(20 on 1g/d, 25 on 750mg/d ,1 on valproate 750mg/d, 3 on Topiramate 50mg/d, 3 on Lamotrigine 100mg/d, 3 on Phenobarbitone 60mg/d, 1 phenytoin 50mg/d . 27 mothers were on >1 AED , of which 20 were on 2 AED and 7 on 3 AED , 28 mothers were on 1 AED only. AEDs were switched in about 20 mothers as soon as pregnancy was confirmed. About 18 moms had other comorbidities like 6 had Intellectual disability, 5 had severe migraine on intermittent paracetamol in pregnancy, 7 had psychiatric conditions like depression, bipolar disorder on Fluoxetine and sertraline. Around 15 underwent C section for obstetric reasons. The type of anaesthesia did not signi cantly in uence the neonatal outcome. Two babies had poor APGAR scores because of maternal general anaesthesia requiring bag and mask ventilation but they recovered within 5 minutes.

Neonatal Outcomes: On comparing the adverse neonatal outcomes in Well and not so well controlled epilepsy , statistically signi cant outcome was found with respect to prematurity only whereas other outcomes were insigni cant **(Table 3)**. Not so well controlled epilepsy had statistically **significant incidence of prematurity P<0.01.**

No statistically significant difference was found in terms of bad neonatal / maternal outcome in those >1 or 1 AED (**Table 4)**. Again on comparing comorbidity and non comorbidity group, among those with 18 moms with comorbidity of which 6 had intellectual disability, 5 had severe migraine on paracetamol and 7 with depression on Selective Serotonin Reupake Inhibitors SSRIs, **statistical significance was found in terms of prematurity P<0.003, LBW P< 0.001 and IUGR P<0.003. (Table 5)**.

Maternal Outcomes: Good outcome, no death or status epilepticus noted in pregnancy. Around 20 had 1-3 episodes of brief convulsions in present pregnancy. Infact some women reported reduced episodes in pregnancy. There was no still birth or abortions too. Due to advent and subsequent widespread use of safer and easily accessible alternative AEDs especially Levetiracetam and Topiramate in Indian market after

early 2000s, Studies done after this period show relatively good outcomes in newborns born to mothers with epilepsy on AED. However the studies dating back from 1950s-1990s before Levetiracetam was popularized may show higher incidence of teratogenicity and pregnancy losses and prematurity, LBW. More awareness on universal intake of folate in pregnancy to prevent adverse neonatal outcomes and congenital anomalies from late 1900s have skewed towards better outcome.

Mazonne[1] made a systematic review and meta-analysis of 8000 articles and found that women with epilepsy have worse perinatal outcomes compared with women without epilepsy in terms of still births, infant deaths, preterms and congenital anomalies as this was skewed, meaning studies were done in late 1900s when newer and safer AED were not yet discovered or used everywhere. Moreover the study reiterated that risks increased with number and dosage of AED used which was consistent with our study where we also showed that prematurity was significant with >1 AED use and those with other serious comorbidities. Viale[3] from their systematic review and metaanalysis of 7000 articles in 2005 also made a similar conclusion that a small but significant association of epilepsy, exposure to antiepileptic drugs and adverse outcomes exists in pregnancy. Indian studies looking into this are too less and almost no major ones from paediatricians. The fewer ones are from obstetrics or neurology. Thomas[6] from neurology, Sree chitra Institute, Trivendrum , in their study of kerala registry of epilepsy and pregnancy from 1998-2013 identified that malformations increased with use of AED numbers, particularly valproate and also clobazam . This is again consistent with our study where the risk increases with increase in number of AEDs. Interestingly however no patient in our study was on clobazam. Meanwhile older studies done in late 1900s showed increased problems due to 1st generation AED usage.

Holmes[9] showed that the physical malformations like midfacial hypoplasia, small head, small body size, increased with more AEDs while those with epilepsy without AED use did not have increased risk. Similarly other studies like Hvas[10] and Neri[8] reiterated similarly that risks increased with polytherapy than epilepsy itself, especially with valproate, Phenytoin, Phenobarbitone. Newer studies with 2nd generation AEDs especially Levetiracetam, Lamotrigine have been reassuring. Levetiracetam was discovered only in 1992 but widely used in 2000s especially in India after 2010 or so in many places. Not many studies were in place too regarding its use in pregnancy, hence not used much till 2010s. Even Congenital malformations were few in our study , mainly were CHDs around 7.

Among the congenital anomalies in our study , majority were CHDs , 7 but not signficant. Study by Thomas[6] from kerala registry[11] had noted that they included atrial septal defect, tetrology of Fallot, patent ductus arteriosus and pulmonic stenosis and ventricular septal defect, tricuspid regurgitation, transposition of great arteries . CHD were significantly more for those with premature birth. They were more frequent with polytherapy compared to monotherapy and also those on 1st line AED. Those with valproate exposure had a trend (not statistically significant) toward higher frequency as compared to others. Dysmorphism in form of midfacial hypoplasia and microcephaly, low ears were seen in 2 only. Other anomalies were meningocele with valproate which is so well known and other 2 were ambiguous genitalia and talipes with levetiracetam and phenobarbitone together and levetiracetam alone respectively .

This low incidence probably was because in many Levetiracetam alone was used and not in high doses and in others with select few another AED had to be added before pregnancy only as epilepsy not controlled with 2 and in 1 on valproate or phenobarbitone, that patient had presented late to us around labour and dose.

Mawhinney[12] study involving a large pregnancy registry from UK involving those on Levetiracetam showed that major malformations are not significant with Levetiracetam monotherapy than with Levetiracetam and Lamotrigine therapy. Levetiracetam when used with valproate or carbamazepine had greater incidence of major malformations . Many in our study were on Levetiracetam (45), of which 38 on monotherapy , 3 with lamotrigine, 1 with topiramate, 2 with phenobarbitone, 1 with phenytoin. Similarly Hoeltzenbein[4] reassured that levetiracetam alone was safe in terms of malformations, IUGR, LBW, Prematurity inspite of high doses and polytherapy especially with valproate or phenobarbitone caused adverse outcomes like malformations. Similarly Wan[13] and Ornoy[14] showed that Lamotrigine and Topiramate even in moderately high doses don't significantly increase major malformations or prematurity respectively and fare better even with Levetiracetam which is reflected in our study too.

The EURAP registry study by Tomson[7,15] have thrown enough light on the safety of Levetiracetam and even with doses of 1g/d is safe as also those like Lamotrigine in doses upto 300mg/d , Carbamazepine CBZ 400mg/d. Risk was high with CBZ >400MG/d and dual therapy with valproate and Phenobarbitone at all doses . In our study too none was on CBZ plus not on such high doses of other AEDs. Chambers[16] studied that women who take fluoxetine during pregnancy do not have an increased risk of spontaneous pregnancy loss or major fetal anomalies, but women who take fluoxetine in the third trimester are at increased risk for perinatal complications like prematurity, IUGR, feeding

difficulties which was consistent with our study wherein those with depression, around 7, were on fluoxetine had significantly low p value with respect to prematurity, LBW IUGR. Similarly Marie Cornett[17] studied that women on Sertraline too had no major malformations but delayed perinatal adaptation like delayed cry , prematurity which is near consistent with our study of association with prematurity. Studies on epilepsy and depression are few like Bjork[18] wherein no significant adverse outcomes were noted in neonates.

Limitations: It was a descriptive study . Our sample size was small around 55 but still data was complete with all details of mom and baby. Since many were on Levetiracetam and not on high doses plus few alone were on 1st line AED, we may not have got significant malformations and other adverse outcomes. Women with poorly controlled epilepsy were excluded from study.

CONCLUSION

Significant association was found between adverse neonatal events in form of Prematurity, LBW, IUGR and comorbidities factors in pregnant women. AED for any one having well controlled epilepsy can be de-escalated as Prematurity was significant in those >1 AED. However dosage did not have a bearing on the outcome. So also there is no significant increase in malformations with any 2nd line AED, especially Levetiracetam in our study though few were on Lamotrigine, Topiramate. Planning pregnancy and switching over to safer AED is important. Treating the comorbidities adequately with safer alternatives is very essential for better outcome.

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