

A Retrospectivestudy of Various Anti-Epileptic Drugs and their Safety in Pregnancy

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ABSTRACT

Antiepileptic drugs used in pregnant women have always been a topic under research, as it involves the safety of both mother and foetus. The aim of the study is to collect various case report of pregnant women and analyse their prescription. The research involves the practical implementation of review of various antiepileptic drugs used in pregnancy. The study of individual cases and CBC fluctuation according to the type of epilepsy and nature of antiepileptic drugs prescribed. To investigate role of folic acid in epilepsy patient monitor the electrolytes fluctuation and change in antiepileptic drugs. To find out the most safest and successful antiepileptic drugs and its adjuvant for pregnant women.

KEYWORDS: Epilepsy types in pregnancy, antiepileptic drugs, safety

INTRODUCTION

I.EPILEPSY AND ITS TYPES:

These are a group of disorders of 5 characterized by paroxysmal cerebral dysrhythmia, manifesting as brief episodes (seizures) of loss or disturbance of consciousness with or without characteristic body movements (convulsions), sensory or psychiatric phenomena. Epilepsy has a focal origin in the brain, manifestations depend on the site of the focus regions into which the discharges spread and postictal depression of these regions. Recognised from the dawn of history as 'disease of lightning', it was correctly described by JH Jackson little over a century ago. Epilepsies have been classified variously; major types as

a. Generalised seizures:

They have a diffuse origin involving both hemispheres of the brain, manifestation and EEG abnormalities are bilateral

i) Generalised Tonic-Clonic Seizures:

(GTCS, major epilepsy grand mal): commonest, lasts 1-2 min. The usual sequence is aura--- cry-unconsciousness and patient fall-tonic spasm of all body muscles--clonic jerking followed by prolonged sleep and depression of all CNS functions.

Absence seizures

(Minor epilepsy, petit mal): prevalent in children, lasts about 1/2 min. momentary loss of consciousness, patient apparently freezes and stares in one direction, no muscular component or little bilateral jerking. EEG shows characteristic 3 cycles per second spike and wave pattern.

Atonic seizures (Akinetic epilepsy):

Unconsciousness with relaxation of all muscles due to excessive inhibitory discharges. Patient may fall

Myoclonic seizures:

Shock-like momentary contraction of muscles of a limb or the whole body.

IV. Infantile spasms (Hypsarrhythmia):

Seen in infants. Probably not a form of epilepsy. Intermittent muscle spasm and progressive mental deterioration. Diffuse changes in the interseizure EEG are noted.

b. Partial seizures :

Simple partial seizures (SPS, cortical focal epilepsy):

Thus the lasts 1/2-1 min. Often secondary. Convulsions are confined to a group of muscles or localized sensory disturbance depending on the area of cortex involved in the seizure, without loss of consciousness.

Complex partial seizures (CPS, temporal lobe epilepsy, psychomotor):

Thus the attacks of bizarre and confused behaviour and purposeless movements, emotional changes lasting 1-2 min along with impairment of consciousness. An aura often precedes. The seizure focus is located in the temporal lobe.

Simple Partial Or Complex Partial Seizures Secondarily generalized:

The partial seizure occurs first and evolves into generalized tonic-clonic seizures with loss of consciousness.

EPILEPSY DURING PREGNANCY :

Hyperemesis gravidarum onset seizure :

Hyperemesis gravidarum (HG) refers to severe nausea and emesis noted during pregnancy. However, no consensus exists on the specific diagnostic criteria that can be used for this condition. The aim of the present systematic review was to summarize the available evidence regarding the severe complications observed during HG with a heightened risk of fatality. A systematic search was conducted on PubMed, Cochrane Library, EMBASE and WILEY databases for the relevant publications regarding the severe and life-threatening complications of HG. The search terms were as follows: '(Hyperemesis gravidarum)' AND ('complications' OR 'severe' OR 'adverse pregnancy outcomes' OR 'stroke' OR 'seizures' OR 'Wernicke's encephalopathy' OR 'arrhythmias' OR 'pneumomediastinum' OR 'coagulopathy' OR 'electrolytic imbalance'). Abstracts, conference presentations, letters to the editor, studies written in languages other than English and editorials were all excluded.

This search identified 43 studies analyzing life-threatening complications of HG, of which 11, seven, eight and 17 articles analyze neurological, cardiovascular, thoracic and systemic complications, respectively. Reports on life-threatening complications were exceptionally rare in HG. The most frequent

severe complications noted were Wernicke's encephalopathy. Hyperemesis gravidarum (HG) is defined as intractable vomiting and nausea during pregnancy. Ptyalism, fatigue, weakness and dizziness are frequent symptoms, whilst rarer symptoms also include hyperolfaction, dysgeusia, decreased gustatory discernment, sleep disturbance, depression, anxiety, irritability and mood changes (1-4). Although >75% of pregnant women suffer from nausea or vomiting during pregnancy, only 0.3-2% pregnant women are diagnosed with HG. The most frequent reasons for hospital admission in women diagnosed with HG include weight loss (>5% pre-pregnancy weight), ketonuria, dehydration, electrolyte imbalance, acid-base imbalances and arrhythmias.

Withdrawal seizures:

Withdrawal-associated seizures are generalized tonic-clonic convulsions that usually occur within 12 to 48 hours after the last alcoholic drink but reportedly sometimes occur after as few as two hours of abstinence. The seizures occur predominantly in patients with a long history of heavy alcohol use, as evidenced by their typical onset during the fourth and fifth decades of life. Withdrawal seizures are usually singular or occur as a brief flurry of seizures over a short period. Recurrent or prolonged seizures or status epilepticus are not typical of withdrawal-associated seizures and should prompt an investigation into possible structural or infectious etiologies, generally guided by the findings of cranial computed tomography (CT), magnetic resonance imaging (MRI), and/or lumbar puncture. Benzodiazepines, phenobarbital, and propofol are recommended in that order to treat status epilepticus while investigations proceed.

Several studies have demonstrated that phenytoin is ineffective in the treatment of alcohol withdrawal seizures, and the drug should not be used for this purpose [14-16]. While some authors use other anticonvulsants such as carbamazepine, valproate, and levetiracetam in the therapy of alcohol use disorder and withdrawal, the role of these medications in alcohol withdrawal-related seizures is incompletely evaluated and therefore cannot be recommended. Although seemingly benign, alcohol withdrawal seizures left untreated progress to delirium tremens (DT) in nearly one-third of patients.

Juvenile Myoclonic Epilepsy:

Juvenile myoclonic epilepsy (JME) is the most common generalized epilepsy syndrome. It is also called Juvenile Myoclonic Epilepsy of Janz. It usually is first seen in adolescence. Less commonly, it can develop in a child who has had childhood absence epilepsy. Juvenile myoclonic epilepsy (JME), otherwise known as Janz syndrome and impulsive petit mal, is an idiopathic, hereditary, and generalized form of epilepsy. It was first described by Herpin in 1867, later on by Janz and Christian in 1957 as 'impulsive petit mal,' and by Lund in 1975 as JME. Its characteristics are the presence of absence, myoclonic, and generalized tonic-clonic seizures. JME falls into the classification of an idiopathic as well as hereditary (positive family history in approximately 50% of cases) disorder. JME is one of the most common childhood/juvenile epilepsy syndromes accounting for approximately 5%-10% of all cases of epilepsy.

JME is seen in both sexes equally, although some studies have reported a higher incidence in females. JME usually manifests between 12 and 18 years of age. JME has both idiopathic and hereditary components. The genetics of inheritance is not fully understood, but a multifactorial mechanism is suspected. CACNB4, EFHC1, GABRA1 are some of the genes that carry known associations with JME.

Although magnetic resonance imaging (MRI) of the brain is unremarkable in classic JME cases, there are reports of structural defects as a possible cause of JME. This activity reviews the evaluation and treatment of juvenile myoclonic epilepsy and the role of the interprofessional team in managing this condition.

Phenytoin-induced seizures:

Phenytoin has become one of the most well-studied anticonvulsants. With an average monthly cost of \$30, it has also become one of the most widely used anticonvulsants, listed on the World Health Organization's List of Essential Medicines. However, with its narrow therapeutic index and its pervasive daily use, considering potential phenytoin overdose or toxicity from chronic use is key to early management and prevention of further toxicity. This activity outlines the medical team's evaluation and management of phenytoin toxicity. Paradoxical seizure is an unusual reaction of seizure aggravation or change in its pattern due to antiepileptics. Decrease in seizure threshold with phenytoin is bound to occur with an increase in serum levels.

We herein report a 51-year-old female, who was brought to the intensive care unit with complaints of episodic seizures and frothing. She is a known case of tonic-clonic epilepsy on oral phenytoin 100 mg for past 6 months. Rapid intravenous infusion of 700 mg phenytoin in 100 mL normal saline over a rate of 15 minutes was initiated on admission. This was followed by a sudden abnormality of her baseline blood parameters and an occurrence of paradoxical seizure. The dose of phenytoin was tapered which reversed her condition. The patient was followed up regularly and monitored for fluctuations in her hematological parameters. The mainstay treatment for phenytoin-induced paradoxical seizure and blood dyscrasias is to monitor the patient and dose titration. Dosing of phenytoin remains a challenge for all clinicians which increase the need for such reports. The incompletely defined convulsant action of phenytoin (PHT) at toxic concentrations in humans. A retrospective chart review (1979–1985) yielded 96 cases (90 patients), meeting both clinical and laboratory criteria for PHT intoxication. Seven patients, all with epilepsy, had one or more seizures while toxic.

However, in only two patients (2.1%) with serum concentrations of 93.2 and 69.7 $\mu\text{g/ml}$ was a causal relationship deemed highly probable. Seizures did not occur in most toxic epileptic patients with total serum PHT concentrations as high as 85.1 $\mu\text{g/ml}$ or in any of the none-epileptic patients with concentrations as high as 64.2 $\mu\text{g/ml}$. The lack of convulsant action of PHT in these patients suggests that seizure risk may be multifactorial and also that PHT is a weak convulsant. We conclude that PHT at very high concentrations can rarely exacerbate seizures or even precipitate generalized status in some epileptic patients, a paradoxical effect.

Gestational hypothyroid seizure:

Thyroid hormones are essential for brain development, and maternal thyroid disease may affect child neurocognitive development. Some types of seizures may also depend upon early exposure of the developing central nervous system, and we hypothesized that maternal thyroid dysfunction could increase the risk of seizure in the child. In a Danish population-based study we included 1,699,693 liveborn singletons, and from the Danish National Hospital Register we obtained information on maternal diagnosis of hyper- or hypothyroidism and neonatal seizure, febrile seizure, and epilepsy in the child.

Maternal diagnosis of thyroid dysfunction before or after birth of the child was registered in two percent

of the singleton births. In adjusted analyses, maternal hyperthyroidism and hypothyroidism first time diagnosed after birth of the child were associated with a significant increased risk of epilepsy in the child. Moreover, hypothyroidism diagnosed after birth of the child was associated with a significant increased risk of neonatal and febrile seizures. No significant association was seen for maternal diagnosis prior to birth of the child. We speculate if some degree of maternal thyroid dysfunction was already present during the pregnancy in mothers diagnosed after birth of the child and if this untreated condition may present a neurodevelopmental risk. Thyroid hormones (THs) l-thyroxine and l- triiodothyronine, primarily known as metabolism regulators, are tyrosine-derived hormones produced by the thyroid gland. They play an essential role in normal central nervous system development and physiological function. By binding to nuclear receptors and modulating gene expression, THs influence neuronal migration, differentiation, myelination, synaptogenesis and neurogenesis in developing and adult brains. Any uncorrected THs supply deficiency in early life may result in irreversible neurological and motor deficits. The development and function of GABAergic neurons as well as glutamatergic transmission are also affected by THs. Though the underlying molecular mechanisms still remain unknown, the effects of THs on inhibitory and excitatory neurons may affect brain seizure activity. The enduring predisposition of the brain to Pathologically, epilepsy may be accompanied by mitochondrial dysfunction, oxidative stress and eventually dysregulation of excitatory glutamatergic and inhibitory GABAergic neurotransmission. Based on the latest evidence on the association between THs and epilepsy, we hypothesize that THs abnormalities may contribute to the pathogenesis of epilepsy. We also review gender differences and the presumed underlying mechanisms through which TH abnormalities may affect epilepsy .

LITERATURE REVIEW

Meador et al. 2007, stated that an anatomical teratogenic mechanism of the AEDs can result in teratogenicity that is either anatomical (MCM) or behavioural (cognitive). Folate deficiency, ischemia, neuronal inhibition, reactive intermediates (such as free radicals and peroxides) and AED-induced neuronal deaths are some of the suggested pathways. The biggest risk of physical problem comes from first-trimester AED exposure, whereas the highest risk appears to be predominantly from third-trimester exposure, suggesting that the mechanisms behind anatomical and teratogenic defects are distinct. Free radical generation is the prevailing theory for the mechanisms causing physical deformities, whereas AED-induced apoptosis and the malfunctions caused in surviving neurons are the major theories for the mechanisms causing behavioural and cognitive dysfunction. The genetic predisposition is at play and that multiple-liability genes may interact with teratogens. (Newman AC, 2017)

Finnell and Chernoff et al. 1987, studied that observed that an individual variability may be partially explained by recent developments in the teratogenic dangers of AEDs that are made possible by the establishment of numerous AEDs in pregnancy registries. Heart malformations, orofacial defects, urologic problems, skeletal abnormalities and neural tube anomalies are the various MCMs. The ventricular septal defect, cleft lip and palate, hypospadias, radial ray defects, phalangeal hypoplasia and spina bifida are few examples for this.

Meador et al. 2008, found that an individual anti-epileptic medication has been linked to anatomical teratogenesis. AEDs have been suspected as teratogenic potentials since 1960s. When compared to other AEDs, carbamazepine has the greatest data regarding pregnancy risk. Holmes and Wyszynski et al. 2004,

found an elevated risk for neural tube defects and cleft lip and palate. Jentink et al. 2010, studied the risk for spina bifida associated with carbamazepine monotherapy, validated by recent major European Surveillance of Congenital Anomalies (EUROCAT) investigation. Although it was lower than valproic acid, carbamazepine's risk was comparable to that of the other AED monotherapies.

Another study, Tomson et al. 2011, research that with his data taken from the EURAP epilepsy and pregnancy registry which is an observational cohort study representing a collaboration of physicians from 42 countries, prospectively monitored pregnancies exposed to monotherapy with different dose of carbamazepine, lamotrigine, valproic acid or phenobarbital, with primary endpoint of MCM detected up to 12 months after birth. This study found dose dependent effect for carbamazepine and also found that risks of malformation were significantly higher with carbamazepine than lamotrigine at doses greater than 400 mg per day. According to a meta-analysis Meador et al. lamotrigine of the newer AEDs, has more data for pregnancy outcomes related to risk of MCMs. The risk of MCM is 2.91%. (Anderson DD, 2012 Tomson et al. 2011, stated that analysed the data from the European and International Registry of Anti-epileptic Drugs in Pregnancy (EURAP) and reported the modified findings. The number of offspring with abnormalities for four monotherapies at various doses up to one year. Monotherapy samples are taken as a birth defect for up to a year. With valproic acid and phenobarbital at examined levels and with carbamazepine at doses greater than 400 mg per day, carbamazepine malformations (up to a year) were considerably higher.

Hunt et al. 2006, studied that described about the levetiracetam-related preliminary findings from the UK Registry showing that 3 of 117 exposed pregnancies (2.7%; 95% CI 0.9-7.7%) had MCMs. Although the sample size is modest and further researches are required to verify these results.

Holmes et al. 2004, research that registered Phenobarbital as major abnormality which was linked to five (6.5%) of 77 fetuses where phenobarbital monotherapy was used. Vajda et al. studied that, foetal phenytoin exposure increased the incidence of birth abnormalities by 10.5%, compared to 4.3% in those who were not exposed to AEDs.

Hunt et al. studied about Topiramate that three of the 70 MCMs found in the UK Registry study of pregnancies exposed to topiramate monotherapy had MCMs. (Grupp SG, 2011).

Harden et al. 2009, stated that made a comparative study with Valproate in comparison to phenobarbital, carbamazepine, phenytoin and lamotrigine, the AAN practice parameters found that valproate monotherapy carried a high risk of MCMs. Due to this danger, the AAN was advised against using valproate during the first trimester of pregnancy. Meador et al. 2008, supports meta-analysis indication, an overall risk of 10.73% for MCMs in children was exposed to valproate in uterus.

According to Arta et al. 2005 and Tomson et al. 2011, the highest risk is posed by doses larger than 1000mg per day of valproate. Use of valproate monotherapy was found to be significantly associated with increased risks for six specific malformations, according to the recent large EUROCAT study. The odd ratios were 12.7 for increased risk for spina bifida, 2.5 for atrial septal defect, 5.2 for cleft palate, 4.8 for hypospadias, 2.2 for poly-dactyl and 6.8 for craniosynostosis. Jentzink et al. 2010, estimated 38 of

1019 newborns (3.7%) who were exposed to lamotrigine in the first trimester, 11 of 393 infants (2.8%) who were exposed to oxcarbazepine, and 5 of 108 infants (4.6%) who were exposed to topiramate had significant birth defects identified. (Wald NJ, 2004) Harden et al. 2009, explained about the levetiracetam (n = 58) and gabapentin (n = 59) exposure during the first trimester was unusual; only 1 (1.7%) and 0 newborns respectively, were found to have birth abnormalities. Polytherapy during the first trimester is likely linked to a higher risk of MCMs. To reduce the incidence of MCMs, the AAN recommended avoiding AED polytherapy if at all possible during pregnancy.

MCMs are particularly at risk from valproate (10.7%). The risk may be higher with phenobarbital (6.5%). Oral cleft risk is increased with topiramate (1.4%). Both valproate (12.7 times) and carbamazepine (2.6 times) enhance the chance of spina bifida. Numerous AEDs have showed dose-dependent hazards, and it's possible that this is true for the entire class of AEDs. Most AEDs and particular polytherapy combinations have unknown absolute hazards.

In the previous ten years, five ASMs—ezogabine, eslicarbazepine, perampanel, brivaracetam and cannabidiol—were approved. There are no published research examining the pharmacokinetics of ezogabine, eslicarbazepine and cannabidiol in pregnant individuals. Eslicarbazepine's teratogenicity was not conclusively proved in one study. A case study of three pregnant women taking brivaracetam revealed no MCMs, but two newborns had three minor congenital abnormalities.

AIM & OBJECTIVE

AIM:

To do a retrospective study of various Anti-epileptic drugs and their safety in pregnant women.

OBJECTIVE:

The main objective of the study is collection of various case reports of pregnant patients and their prescribed Anti Epileptic Drugs (AEDs).

A comparative study of highly prescribed Antiepileptic drugs which is meant to be much safe.

To analyse the influence of folic acid dose before and after pregnancy patients.

To collect the safety report of AED and tetragenecity.

METHODOLOGY

CASE STUDIES

The case study have been done individually in our institution (Tagore medical college and hospital). Totally TEN cases have been reported. These cases have been compared and studied for the effective outcome of the review article which was our earlier study.

CASE-I:

The patient is of 19 years female P1L1A1 has a history of seizures occurrence during second trimester. The LBC involves TC range of 16900, HB-11.2, PCV-35, Na-131, K+ -4.8. The vitals as BP-100/60 mm/Hg, PR-72/Min, SPO2 -99% Temperature normal. The drugs prescribed were Ampicillin-500mg IV BD, Metronidazole-250mg TDS, T. Para BD, injection Lorazepam 20mg/10ml, injection Heparin-500000 UI.

CASE-II:

This patient is of 23 years female in gestational period of 10 week 4 days, Diagnosed with Hyperemesis Gravidoma/Bicytopenia after CBC reports, TC-7400, Platelet-25000, HB-7.7, PCV-24, DC-17.7, RBS-113, Na-138, K+ -3.6, Her vitals as reports BP-110/60 mm/Hg, PR- 92/Min, SPO2 -98% Temperature normal .She had symptoms of vomiting,headache,increases episodes of seizure. The prescription shows IVF,RC, Injection Ceftriaxone -1g BD, Injection Ondansetron, Injection Thiamine - 100mg, Injection Pan-100mg ,Levitiracetam-500mg TDS.

G - Gravida, how many times patient conceived P – Para, how any pregnancy crossed viability L – Live baby

A – Abortion

CASE-III:

The case-III is of 25 years female in gestation of 35 weeks and 2 days reported with 2 episodes of seizures in 2 days and palpitation. Diagnosed as withdrawal seizures. The CBC reports TC-8600, HB-8.4, PCV-28 and the vitals are BP-120/80 mm/Hg, PR-28/Min, SPO2 - 98% Temperature normal. The drugs prescribed as Injection Ceftriaxone-1g IV BD, Injection Phenytoin-100mg TDS , T. Levitiracetam-500mg TDS , Injection Dexamethasone-6mg IV BD.

CASE-IV:

The case-IV is of 22 years female under 3 weeks 1 day gestation . The CBC report as TC- 10300, HB-10.9, PCV-2, Na-133mg/l, K+ - 42, and the vitals are BP-100/60 mm/Hg, PR- 98/Min, SPO2 - 98% Temperature normal .Diagnosed as Juvenile Myoclonic epilepsy . The drugs prescribed Injection Levitiracetam-500mg TDS , T. Clobazam-10mg, T. Folic acid - 5mg DD Injection Lorazepam- 0.5 mg.

CASE-V:

The case-V is of 18 years female, P1L1A1, The CBC shows TC-13900, HB-10.8, PCV- 31,RBS-94, Na-135, K+ -3.7. The vitals shows are BP-90/60 mm/Hg, PR-101/Min, SPO2- 98% Temperature normal. Diagnosed as seizures, hypothyroid .The drug given way Injection Phenytoin-100mg, T. Eltroxin-25mg, T. Calcium, T. BCT.

CASE-VI:

The case-VI is of 26 years female in the third trimester of gestation who is P1L1A1. The CBC report is TC-6700, HB-10.5, PCV-32,RBS-94,Na-128,K+ -2.8.The vital shows are BP-110/70 mm/Hg, PR-84/Min, SPO2 -99% Temperature normal. Diagnosed as break through phenytoin induced seizure .The drug chart was prescribed as T. Levitiracetam-750mg BD, T. Carbamazepine-200mg, T. Clobazam-5mg BD, Injection Midazolam- 0.1 mg/kg .Had a history of high doses of folic acid during first12 weeks of pregnancy.

CASE-VII:

The case-VII is of 22 years female in the gestation period of 10 weeks 4 days. The CBC reports shows as TC8800, HB-8.7, PCV-26,PLC-20000, Na-140, K+ -3.3. The vitals shows are BP-120/80 mm/Hg,PR-77/Min,SPO2 - 98% Temperature normal. Diagnosed with new onset of seizure and hyperemesis gravidoma ,symptoms includes uprolling of eyeballs, vomiting, fever, cough, tongue bite. The drugs

prescribed Injection Ceftriaxone-1g IV BD,, Injection Thiamine- 500mg in 100 ml,Injection Ondansetron,Injection Pan, T.Paracetamol, T.Cetirizine, Injection Phenytoin -100mg TDS.

CASE-VIII:

The case-VIII is of 26 years female in the gestation of P1L1A1. The CBC shows as HB- 13.6, RBS-63. TSH before pregnant 2.14 after pregnant 4.49. The vitals shows are BP-110/50 mm/Hg, PR-90/Min, SPO₂ - 97% Temperature normal, RR-18. The symptoms include drowsiness. Diagnosed as Phenytoin induced focal multiple episodes. The drugs prescribed as T. Levitiracetam-750 mg BD, T. Carbazepine-200mg, T. Clobazam-5mg BD, Injection Midazolam- 0.1 mg/kg.

CASE-IX:

The case-IX is of 25 years female Rh-negative in the G2P0L0A1C epilepsy. The CBC reports shows as TC-300000, TSH-2%, HB-13.6 gm, Na-137, K+ - 4.4. Delivery healthy baby weight has 3.4 kg. The drugs prescribed as T. Levipill-750 mg BD, T. Lobazam-5mg BD, T. Lacosamide-50g BD.

CASE-X:

The case-X is of 25 years female Rh-negative in the G2P1L1 stage with 31 weeks 5 days pregnant, gestational hypothyroid with medication with medication as T. Levipill-750 mg BD, T. Lobazam-5mg BD, Folic acid-5mg till a history baby died in wombs at 8 months.

HIGHLY PRESCRIBED ANTI-CONVULSANT DRUG IN PREGNANCY

Though list of drugs have been studied for AEDs in pregnancy practical application of drugs based on patient experience is much beneficial the safety perspective. As oldest traditional drugs as a basic Phenytoin have also been used in first line drug in most of the patient. In the sequence, Levitiracetam have been widely prescribed to large amount of population due to its high safety profile. As a immediate reverse therapy, lobazam, miconazole, lorazepam have been widely prescribed. The Antiepileptic drugs Carbamazepine have been used only in the stage of alternative purpose of alternative purpose only in utmost needed condition.

HIGHLY PRESCRIBED ADJUVANT DRUGS IN AEDs USED DURING PREGNANCY

The most essential adjuvant used in all the trimester of pregnancy is folic acid, B-Complex, Thiamine. Based on the type of seizures other adjuvants such as Eltroxins, Lacosamide becomes essential adjuvant.

SAFETY OF HIGHLY PRESCRIBED AEDs IN PREGNANCY :

Phenytoin in pregnancy:

Phenytoin (Dilantin) is an older, first-generation AED. In adults, adverse effects can include peripheral neuropathy, vitamin D and K deficiencies, and folate deficiency with resultant megaloblastic anemia. Gingival hyperplasia develops in more than 45% of users. A pattern of fetal anomalies associated with hydantoin, of which phenytoin is a derivative, was first described in the literature. The characteristics of fetal hydantoin syndrome include IUGR with small head. Midwives are likely to encounter a pregnant woman with epilepsy, one of the most common neurological conditions of women who are of reproductive

age, which affects around 0.3% to 0.5% of pregnancies. Phenytoin, an FDA category D medication, is one of the most commonly prescribed AEDs. Studies indicate that around 1:200 pregnant women are exposed to AEDs, including phenytoin.

Safety of phenytoin:

The phenytoin has been used as a traditional drug. But its safety profile limits, depending upon the concentration of phenytoin in plasma. When the plasma concentration more than 30 mg its limitation has been considered.

Phenytoin induced convulsions:

From the case study VI and VIII there is evidence for phenytoin induced convulsion during pregnancy. In both the study this type of convulsions occurred after prolonged use of phenytoin till second trimester. Once the third trimester reached the phenytoin profile usage causes evident changes in the electrolytes, that is decreased profile in potassium levels (K^+), which needs alternatives (AE drugs) in third trimester.

Levetiracetam in pregnancy:

Levetiracetam is a broad-spectrum antiepileptic drug (AED) which is currently licensed in the United States and the United Kingdom and Ireland for use as adjunctive treatment of focal-onset seizures and myoclonic seizures or generalized tonic-clonic seizures, occurring as part of generalized epilepsy syndromes. In the United Kingdom and Ireland, it is also licensed as monotherapy treatment for focal-onset seizures. Previous small studies have suggested a low risk for major congenital malformations (MCM) with levetiracetam use in pregnancy. This study, in a meaningful number of exposed pregnancies, confirms a low risk for MCM 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. Levetiracetam profile introduction due to the metabolism of levetiracetam differ from other drug, it has been widely used. Among the 10 case studies, Levetiracetam is the mostly prescribed drug.

Carbamazepine in pregnancy:

Carbamazepine (CBZ) has been used as an effective treatment of seizures, bipolar disorder, and certain types of pain. Carbamazepine has been viewed by many as the antiepileptic drug (AED) of choice during pregnancy, as there are more studies on the fetal outcomes associated with in utero CBZ monotherapy compared with other AEDs. Treatment of active epilepsy is important during pregnancy because seizures can lead to falls, injury, and physical stress that can endanger the health of the woman and the fetus. Carbamazepine has not been associated with increased risk of pregnancy complications such as cesarean section, preeclampsia, or premature delivery,⁴ and its contributions to congenital malformations and neurodevelopmental anomalies have become clearer owing to recent large studies. Carbamazepine is a medication that has been used to control seizures. It has also been used to treat other conditions, such as bipolar disorder, schizophrenia, or pain disorders. If carbamazepine can make it harder to get pregnant. Carbamazepine profile introduction from the case study of 6 and 8 carbamazepine has been prescribed as alternative to phenytoin in 3rd trimester of pregnancy. Carbamazepine least prescribed drug next to sodium

valproate. Carbamazepine have been shown safety profile when used along with Levitiracetam. Carbamazepine have been considered to prescribe only doctor's advice, when there is no choice of other AED during in particular situation. The safest range of carbamazepine during pregnancy is only considered after 16 weeks of pregnancy only when it is needed, in no other choice of drug category.

Benzodiazepines roles in AED:

Benzodiazepines (BZDs) are the first-line treatment for SE worldwide due to their efficacy, tolerability, and rapid onset of action. Benzodiazepines are commonly prescribed as anxiolytics, sedatives, and anticonvulsants. They act on the GABAA receptor by increasing the conductance chloride through ionic channels, promoting a state of central nervous system depression. The clinical properties of benzodiazepines are dependent upon the composition of the different subunits of the GABAA receptor. Each subunit, in turn, has multiple subtypes that are present throughout the central nervous system, all of which impart different clinical responses. Benzodiazepines are the first-line treatment of status epilepticus. Time to treatment is crucial, and clinical response to benzodiazepines is lost with prolonged status epilepticus. Non-intravenous routes of midazolam should be considered as an equally efficacious alternative to intravenous lorazepam, which is the most commonly administered benzodiazepine for status epilepticus when intravenous access is available.

The conventional BZDs clonazepam, diazepam, lorazepam and midazolam differ mainly in their durations of action and available routes of administration. In addition to the common intravenous, intramuscular and rectal administrations that have long been established in the acute treatment of SE, other administration routes for BZDs—such as intranasal administration—have been developed in recent years, with some preparations already commercially available. Most recently, the intrapulmonary administration of BZDs via an inhaler has been investigated.

This narrative review provides an overview of the current knowledge on the efficacy and tolerability of different BZDs, with a focus on different routes of administration and therapeutic specificities for different patient groups, and offers an outlook on potential future drug developments for the treatment of prolonged seizures and SE.

The Midazolam, Alprazolam, Lobazam all comes Benzodiazepine category.

Role of midazolam in convulsion profile:

Midazolam is used for the induction of anesthesia and also in the management of acute seizures. Because of its water-soluble nature, midazolam has a rapid onset of action and can be used to manage status epilepticus when intravenous administration of other medications is not feasible. Midazolam can be used for anxiolysis and hypnosis during the maintenance phase of general anesthesia. Midazolam is an adjunct medication to regional and local anesthesia for a wide range of diagnostic and therapeutic procedures and has greater patient and clinician acceptance. This activity will highlight the mechanism of action, adverse event profile, pharmacology, monitoring, and relevant interactions of midazolam, pertinent for members of the interprofessional team in the treatment of patients where it is of clinical value. Midazolam is seen to be an effective agent in the emergency treatment of seizures.

Role of Alprazolam in convulsion profile:

Alprazolam is frequently prescribed to manage panic and anxiety disorders..Alprazolam is categorized as pregnancy category D medicine. Maternal exposure to alprazolam in the later trimester of pregnancy may

result in sedation (lethargy, respiratory depression, hypotonia) and withdrawal symptoms (irritability, hyperreflexia, restlessness, tremors, feeding difficulties, and inconsolable crying, and) in the neonate. As benzodiazepines can cross the placenta, clinicians should observe newborns for signs/symptoms of sedation, respiratory depression, feeding problems, and neonatal withdrawal syndrome and manage them appropriately. Available data of published observational studies of pregnant women exposed to alprazolam have not related alprazolam-associated risk of miscarriage, major congenital disabilities, or adverse maternal or fetal outcomes.

Use of alprazolam late in pregnancy can result in sedation (respiratory depression, lethargy, hypotonia) and/or withdrawal symptoms (hyperreflexia, irritability, restlessness, tremors, inconsolable crying, and feeding difficulties) in the neonate. Monitor neonates exposed to alprazolam during pregnancy or labor for signs of sedation and monitor neonates exposed to alprazolam during pregnancy for signs of withdrawal; manage these neonates accordingly.

Role of Lobazam in convulsion profile:

Lobazam suppresses the abnormal and excessive activity of nerve cells of the brain. It is used to treat epilepsy (seizures) and severe anxiety. It also reduces tiredness, feeling of restlessness, difficulty in concentration, and irritation. Thus, helping in living an uninterrupted normal lifestyle. Lobazam tablets is a category C drug, which may have potential side effects on the foetus and can be unsafe to use during pregnancy. Seek advice from an expert in cases of emergency. Limited studies on Lobazam show defective effects on the foetus (teratogenic or embryocidal), so its safety for the foetus is questionable.

Still, the doctor will check the benefit to risk ratio before prescribing it to the pregnant female. It can also help reduce symptoms of seizures, such as confusion, uncontrollable jerking movements, loss of awareness, and fear or anxiety.

This medicine can allow you to do some activities that you would otherwise be forbidden or scared to do (such as swimming and driving). It can take a few weeks for this medicine to work (because the dose has to be increased slowly) and during this time you may still have seizures. Therefore, do not stop using this medicine even if you feel well, until your doctor advises you to. Missing doses may trigger a seizure. It may be unsafe to use during pregnancy. Although there are limited studies in humans, animal studies have shown harmful effects on the developing baby. That doctor will weigh the benefits and any potential risks before prescribing it.

These 3 drugs are utilized mainly for the ready onset of action and reverse ability which facilitate to control the onset of epilepsy by acting centrally.

SAFETY OF HIGHLY PRESCRIBED ADJUVANT OF AEDs IN PREGNANCY.

Folic acid, B-Complex, Thiamine, helps in elevating the haemoglobin profile of the patients, which is the major causes of Hyperemesis gravidarum seizures.

Role of folic acid :

Folic acid is crucial for proper brain function and plays an important role in mental and emotional health. It aids in the production of DNA and RNA, the body's genetic material, and is especially important when cells and tissues are growing rapidly, such as in infancy, adolescence, and pregnancy. Folic acid also works closely with vitamin B12 to help make red blood cells and help iron work properly in the body. Pregnant women need more folic acid to lower the risk of neural tube birth defects, including cleft palate, spina

bifida, and brain damage. Neural tube defects are birth defects caused by abnormal development of the neural tube, a structure that eventually gives rise to the brain and spinal cord. Since folic acid has been added to many grain foods in the U.S., such as bread and cereal, neural tube defects have decreased dramatically.

When the baby is developing early during pregnancy, folic acid helps form the neural tube. Folic acid is very important because it can help prevent some major birth defects of the baby's brain (anencephaly) and spine (spina bifida). The neural tube forms the early brain and spine. Birth defects occur within the first 3-4 weeks of pregnancy. So it's important to have folate in your system during those early stages when your baby's brain and spinal cord are developing. If you talked to your doctor when you were trying to conceive, they probably told you to start taking a prenatal vitamin with folic acid. One study showed that women who took folic acid for at least a year before getting pregnant cut their chances of delivering early by 50% or more.

The CDC recommends that you start taking folic acid every day for at least a month before you become pregnant, and every day while you are pregnant. However, the CDC also recommends that all women of childbearing age take folic acid every day. So you'd be fine to start taking it even earlier. If you picked out your own prenatal vitamin, take it to your OB once you're pregnant to make sure it has the recommended amounts of everything you need, including folic acid. All prenatal vitamins are not the same and some may have less or more of the vitamins and minerals. Dietary supplementation with folic acid around the time of conception has long been known to reduce the risk of NTD in the offspring.

Role of B-Complex :

B vitamins, also known as B-complex vitamins, play essential roles in catabolic and anabolic metabolism. These 8 water-soluble vitamins are excreted in urine and require repletion daily. The B vitamins are identified as follows: thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folate (B9), and cobalamin (B12). B vitamins act as coenzymes in several enzymatic processes that support every aspect of cellular physiological functioning, including major functions within the brain and nervous system. Any B vitamin deficiency can negatively affect mitochondrial metabolism of amino acids, glucose, and fatty acids through the citric acid cycle and electron transport chain. B vitamins are especially important for those who are pregnant or breastfeeding. These vitamins aid in fetal brain development, and they reduce the risk of birth defects.

B-1 (Thiamine): 1.4 mg – Supports baby's healthy brain development
B-2 (Riboflavin): 1.4 mg – Keeps eyes healthy and skin glowing

B-3 (Niacin): 18 mg – Eases morning sickness, keeps nausea at bay and improves digestion

(Pantothenic Acid): 6 mg – Reduces leg cramps and helps produce essential pregnancy hormones

(Pyridoxine): 25 – 50 mg – Aids the development of baby's nervous system and brain (don't exceed 100 mg)

(Biotin): 30 mcg – Deficiency is often caused by pregnancy, so increased consumption is vital

B-9 (Folic Acid): 400 – 800 mcg – Plays a huge role in reducing the risk of birth defects (don't exceed 1000 mcg)

B-12 (Cobalamin): 2.6 mcg – Maintains and supports the development of you and your baby's nervous system

Role of Thiamine :

Thiamine is one of the B vitamins. The B vitamins are a group of water-soluble vitamins that are part of many of the chemical reactions in the body. It has a function in Thiamine (vitamin B1) helps the body's cells change carbohydrates into energy. The main role of carbohydrates is to provide energy for the body, especially the brain and nervous system. Thiamine also plays a role in muscle contraction and conduction of nerve signals. Thiamine is essential for the metabolism of pyruvate, which is an important molecule in several chemical reactions in the body. Thiamine is present naturally in some diets or added to some food products and provided in the form of dietary supplements.

During energy metabolism, thiamine plays a critical role in the human body. Thiamine is actively absorbed and passively diffused by the small intestine at nutritional and pharmacological doses. It also helps your nervous system, muscles, and heart function normally and is essential for your baby's brain development. Thiamine vitamin, is needed for glucose metabolism enabling you and your baby to use carbohydrates as energy . In pregnancy, thiamine plays a major role in the development of the baby's brain. It's also essential for proper nerve, muscle, and heart function for both the mother and baby. Like all the B vitamins, thiamin is a water-soluble vitamin, meaning the body does not store them.

Some additional vitamin b1 benefits are strengthening the immune system and improving the body's ability to tolerate stressful conditions . Some people even call it the "anti-stress" vitamin it is an essential nutrient for the healthy development of the fetus and has many health benefits. The recommended daily intake of thiamine during pregnancy is 1.4 mg per day for all ages. Women carrying more than one fetus may need a high dose of thiamine. During pregnancy, thiamine is sent to the fetus via the placenta. Pregnant women have a greater requirement for the vitamin than other adults, especially during the third trimester. Pregnant women with hyperemesis gravidarum are at an increased risk of thiamine deficiency due to losses when vomiting. In lactating women, thiamine is delivered in breast milk even if it results in thiamine deficiency in the mother. Thiamine is important not only for mitochondrial membrane development, but also for synaptic membrane function. It has also been suggested that a deficiency hinders brain development in infants and may be a cause of sudden infant death syndrome. Eltroxin prescribed as adjuvant depending upon the hyperthyroidism condition. There have been studies about seizure induction due to low thyroid in pregnancy.

Role of Lacosamide in pregnancy:

Lacosamide (LCM) is a third-generation anti-seizure drug (ASD) used in the treatment of both focal onset seizures and primary generalized tonic-clonic seizures. Still considered a new ASD, teratogenicity from LCM exposure during pregnancy is unknown, thereby designated as Category C in safety. In the recent December 2020 update by the North American Anti-Epileptic Drug (NA-AED) registry, of 65 monotherapy LCM uses during pregnancy, none were associated with major congenital malformations MCMs. Lacosamide is indicated for the treatment of partial-onset seizures and adjunctive therapy in the treatment of primary generalized tonic-clonic seizures.

CBC ANALYSIS OF ANTI-EPILEPTIC DRUGS DURING PREGNANCY

When analysing the complete blood count report of all the nine case study it shows a comparative result. In case 2 it shows decreased HB value of 7.7 and PCV also dropped to This helps in diagnosis of Hyperemesis gravidoma and shows the importance of folic acid supplement in hyperemesis gravidoma seizure. Similarly in case-III, even in third trimester , during withdrawal seizure

also HB value drops 84 and PCV =28, shows the need of folic acid. In case-VIII similar like case-III, the HB value drops 8.7 and PCV shows 2.6 . While studying the electrolyte profile .In case study 6 phenytoin induced seizure, there shows a marked decreased in K⁺ level 2.8 and slight decreased in Na⁺ level.

Role of potassium electrolyte in convulsion:

Electrolyte homeostasis in the central nervous system(CNS) is essential for brain function. Regulation of ionic balance is a critical process involving a complex array of molecules for moving ions into and out of the brain and involving blood–brain barrier function as well as mechanisms in the membranes of both neurons and glia. Alterations in ion gradients across cellular membranes can have direct and indirect effects on neuronal discharge and may facilitate epileptiform activities. A variety of pathological states or conditions such as dehydration or renal failure are associated with substantial modifications of plasma osmolality and electrolyte balance. These conditions may overcome homeostatic brain systems and provoke profound consequences on brain metabolism and function. Other electrolyte alterations, hypokalemia or hyperkalemia rarely causes symptoms in the CNS, and seizures do not occur. Changes in the extracellular potassium level (serum levels) have predominant and profound effects on the function of the cardiovascular and neuromuscular systems.

Thus severe potassium abnormality may provoke fatal arrhythmias or muscle paralysis before CNS symptoms appear .In summary, seizures often represent an important clinical manifestation of electrolyte disturbances. Seizures are more common in patients with sodium disorders, hypocalcemia, and hypomagnesemia. Successful management of patient seizures begins with the establishment of an accurate diagnosis of the underlying electrolyte disturbances. For that reason, complete serum chemistry, including measurements of electrolytes, especially sodium, calcium, and magnesium, should be part of the initial diagnostic workup in adult patients with seizures.

Early identification and correction of these disturbances are necessary to control seizures and prevent permanent brain damage, as AEDs alone are generally ineffective. All physicians should be aware of these clinical conditions and have an understanding of the underlying medical disorders, for this may provide the means of controlling the disease and initiate a rapid and appropriate therapy..

ROLE OF THYROID AND CONVULSION IN PREGNANCY :

In case study-V, thyroid epileptic patient study have been done . In this a similar profile have also been studied in case study-IX , Finding are there which shows decreased thyroid profile induced seizures.

Thyroid hormones are crucial for normal development of the baby's brain and nervous system. During the first trimester—the first 3 months of pregnancy baby depends on your supply of thyroid hormone, which comes through the placenta NIH external link. At around 12 weeks, your baby's thyroid starts to work on its own, but it doesn't make enough thyroid hormone until 18 to 20 weeks of pregnancy. Two pregnancy-related hormones—human chorionic gonadotropin (hCG) and estrogen—cause higher measured thyroid hormone levels in your blood. The thyroid enlarges slightly in healthy women during pregnancy, but usually not enough for a health care professional to feel during a physical exam. Thyroid problems can be hard to diagnose in pregnancy due to higher levels of thyroid hormones and other symptoms that occur in both pregnancy and thyroid disorders.

Some symptoms of hyperthyroidism or hypothyroidism are easier to spot and may prompt your doctor to test you for these thyroid diseases. Another type of thyroid disease, postpartum thyroiditis, can occur after your baby is born. Hyperthyroidism in pregnancy is usually caused by Graves' disease and occurs in 1 to

4 of every 1,000 pregnancies in the United States.¹ Graves' disease is an autoimmune disorder. With this disease, your immune system makes antibodies that cause the thyroid to make too much thyroid hormone. This antibody is called thyroid stimulating immunoglobulin, or TSI. Graves' disease may first appear during pregnancy. However, if you already have Graves' disease, your symptoms could improve in your second and third trimesters. Some parts of your immune system are less active later in pregnancy so your immune system makes less TSI.

This may be why symptoms improve. Graves' disease often gets worse again in the first few months after your baby is born, when TSI levels go up again. If you have Graves' disease, your doctor will most likely test your thyroid function monthly throughout your pregnancy and may need to treat your hyperthyroidism.¹ Thyroid hormone levels that are too high can harm your health and your baby's. hyperthyroidism during pregnancy is associated with increased maternal and perinatal morbidity. Some features of this disease simulate preeclampsia, which may encourage delivery of the fetus. We report a case of poorly controlled hyperthyroidism associated with generalized seizures, where patient management was directed at a diagnosis of preeclampsia-eclampsia. Although the presence of eclampsia and marked hyperthyroidism is very rare, this case illustrates the importance of aggressive medical management of hyperthyroidism.

A 17-year-old gravida was diagnosed with hyperthyroidism at 15 weeks' gestation. At 26 weeks' gestation, she was admitted to the hospital after noting edema of the upper and lower extremities, nausea, vomiting, shortness of breath, and a cough. At admission, she was hypertensive, tachycardic, and dyspneic. The patient was believed to have preeclampsia with pulmonary edema complicated by hyperthyroidism. We initiated magnesium sulfate therapy and administered several bolus doses of hydralazine, with little effect on blood pressure. Oliguria was noted, and a pulmonary artery catheter was inserted. Hours later, generalized seizure activity occurred, and a decision was made for abdominal delivery. Postoperatively, cardiovascular function stabilized.

On postoperative day 3, we received the results of the thyroid function tests obtained at admission, which suggested a markedly hyperthyroid condition. Untreated or poorly treated hyperthyroidism may present a clinical picture similar to preeclampsia. In our case, both disease processes coexisted in their severest forms. It is possible, although completely unproven, that a relationship exists between poorly controlled hyperthyroidism and preeclampsia-eclampsia. More importantly, accurate diagnosis of hyperthyroidism should lead to prompt medical or surgical management, thereby decreasing maternal and perinatal morbidity. Hypothyroidism in pregnancy is usually caused by Hashimoto's disease and occurs in 2 to 3 out of every 100 pregnancies.¹ Hashimoto's disease is an autoimmune disorder. In Hashimoto's disease, the immune system makes antibodies that attack the thyroid, causing inflammation and damage that make it less able to make thyroid hormones.

ROLE OF BLOOD PRESSURE AND AEDs IN PREGNANCY :

BP roles is very important in the induction of seizure. There are more studies regarding the vascular study role in convulsion . In case study-V ,BP have been reduced to 90/60 in hypothyroid profile seizure.

i. Role of BP in hypothyroid:

Hypothyroidism can affect the heart and circulatory system in a number of ways. Insufficient thyroid hormone slows your heart rate. Because it also makes the arteries less elastic, blood pressure rises in order to circulate blood around the body. Elevated cholesterol levels, which contribute to narrowed, hardened arteries, are another possible consequence of low thyroid levels. Another noncardiac symptom—muscle

aches—may also be relevant. Muscle aches can be a symptom of hypothyroidism as well as a side effect of cholesterol-lowering statin medications, a condition known as statin-related myalgia. In fact, research suggests that hypothyroidism is more common in people who can't tolerate statins.

Sometimes treating hypothyroidism helps relieve statin-related myalgia. Elevated diastolic blood pressure is present in ~30% of patients with overt hypothyroidism. Cardiac contractility and output decreases leading to a narrowed pulse pressure. In hypothyroidism renin release is decreased with an increased salt sensitivity. The consequent renal sodium reabsorption leads to an expansion of blood volume by 5.5%. Hypothyroidism has been known to be associated, at times, with diastolic hypertension. In 40 thyrotoxic patients that the induction of hypothyroidism by radioiodine therapy significantly increased diastolic blood pressure.

DRUG SAFETY OF AED DURING PREGNANCY

Report have been shown in case study 8 with profile of AED drugs prescribed with levitiractam and lobazam with folic acid alone during the pregnancy period . folic acid have been prescribed even for the post partum pregnancy along with seizure medication.

RESULTS & DISCUSSION

Graphical representation reference for the mentioned CBC profile & explanation . graphical representation for the mentioned vital profile. Graphical representation for electrolyte profile pie chart representation of highly prescribed AED in pregnancy & explanation.

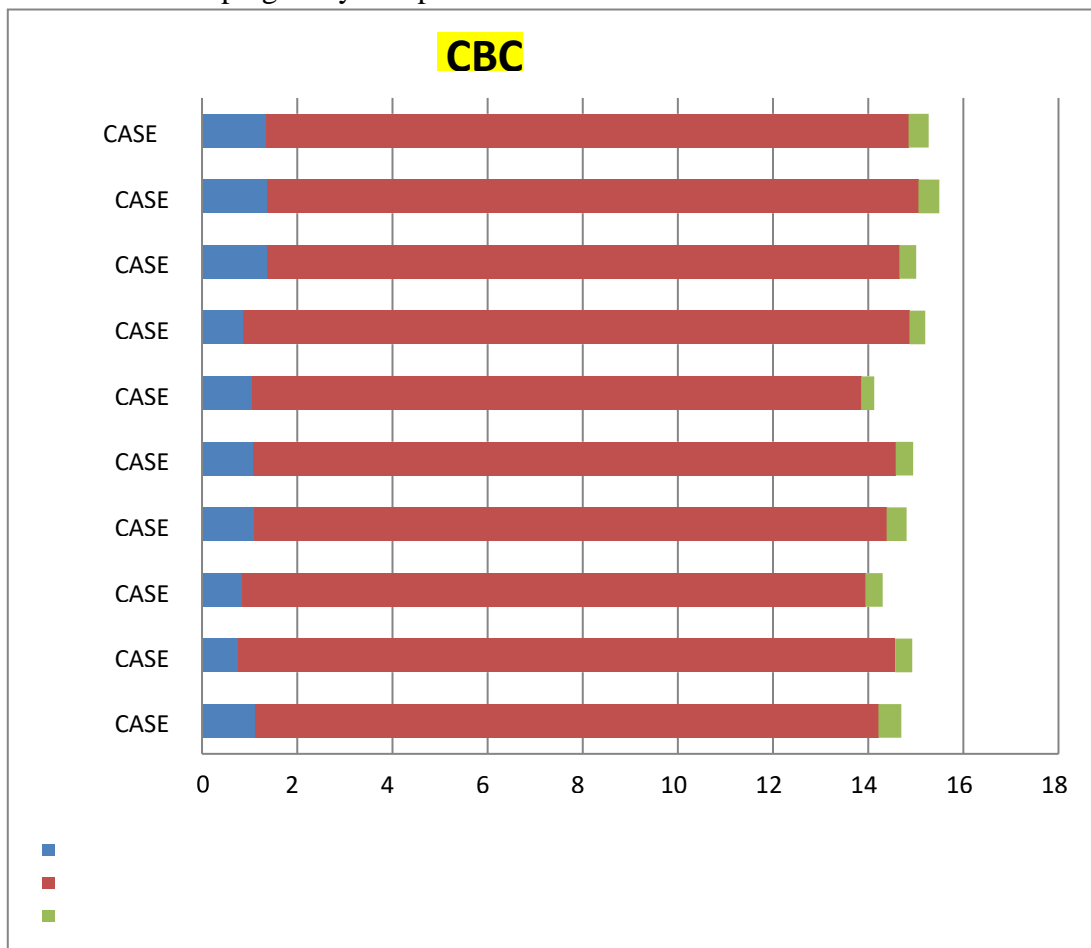


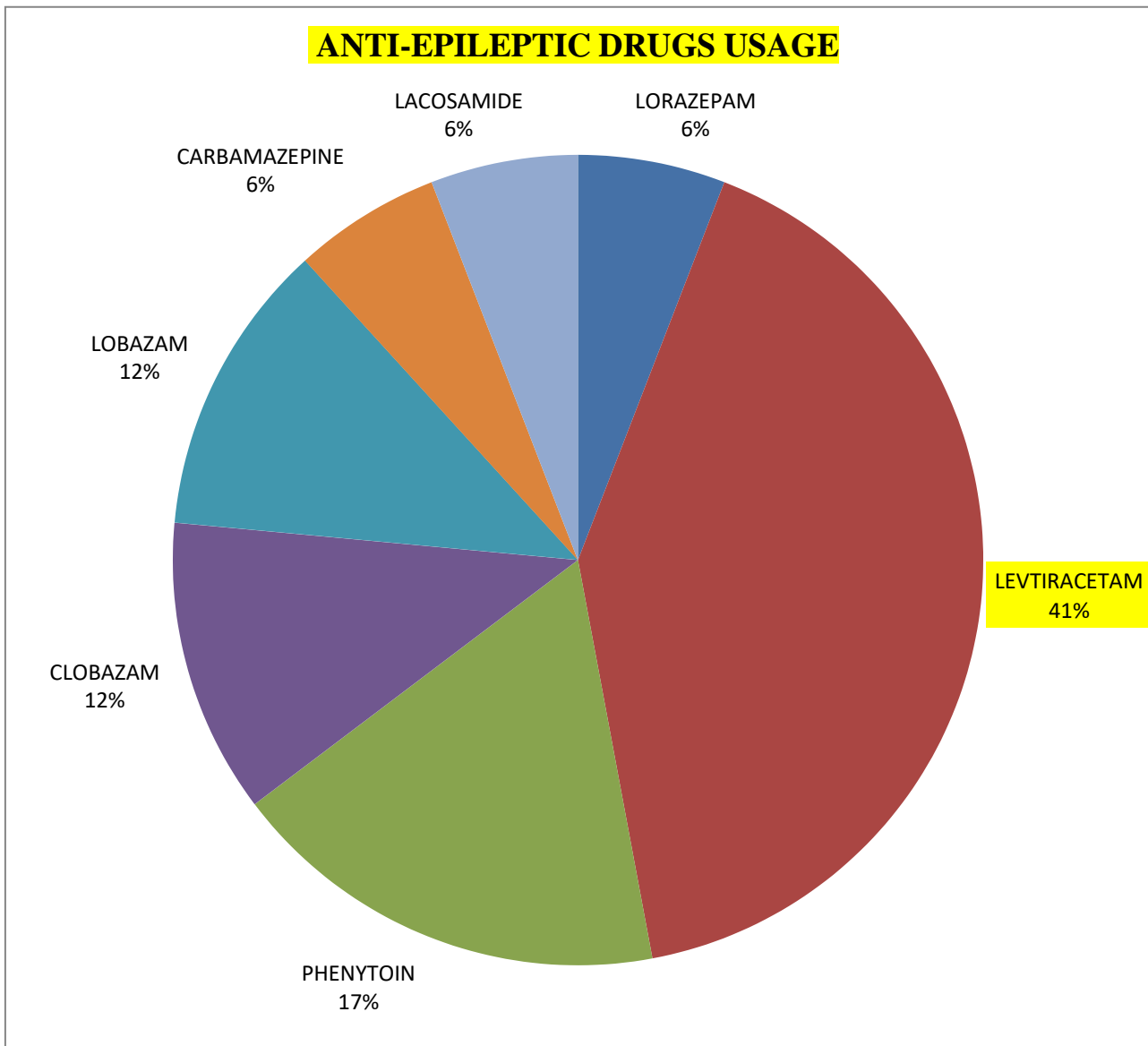
FIG.1. BAR GRAPH REPRESENTATION FOR CBC PROFILE :

	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5	CASE 6	CASE 7	CASE 8	CASE 9	CASE 10
HEMOGLOBIN	11.2	7.7	8.4	10.9	10.8	10.5	8.7	13.6	13.6	13.5
SODIUM	131	138	131	133	135	128	140	133	137	135
POTASSIUM	4.8	3.6	3.7	4.2	3.7	2.8	3.3	3.5	4.4	4.2

From the bar graph, it is evident that, cases 2, 3 and 7 show a low profile in hb value, which is an indication of hyperemesis gravidarum seizure.

Case 3 and 6 show a low profile in Na level & Case 6 shows a low K level profile shows phenytoin induced seizure.

FIG.2. PIE CHART REPRESENTATION FOR ANTI-EPILEPTIC DRUGS USAGE :



From the pie chart, the most prevalent anti-epileptic drug during pregnancy is LEVTIRACETAM. From the case study VI and VIII there is evidence for phenytoin induced convulsion during pregnancy. In both the study this type of convulsions occurred after prolonged use of phenytoin till second trimester.

Once the third trimester reached the phenytoin profile usage causes evident changes in the electrolytes, that is decreased profile in potassium levels (K⁺), which needs alternatives (AE drugs) in third trimester.

Carbamazepine profile introduction from the case study of 6 and 8 carbamazepine has been prescribed as alternative to phenytoin in 3rd trimester of pregnancy. Carbamazepine least prescribed drug next to sodium valproate. Carbamazepine have been shown safety profile when used along with Levitiracetam. Carbamazepine have been considered to prescribe only doctor's advice, when there is no choice of other AED during in particular situation. The safest range of carbamazepine during pregnancy is only considered after 16 weeks of pregnancy only when it is needed, in no other choice of drug category.

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CONCLUSION

Based on the research study the comparative study of review plays similar and wide for levitiracetam drug. The limitation of phenytoin have been studied. Lamotrigine which has been studied in review doesn't have much practical applications when compared to other AED'S. sodium valproate must not be used in AED during pregnancy is reconfirmed. The use of carbamazepine only during withdrawal of phenytoin is much employed. In terms of adjuvant drug folic acid proves to be the essential adjuvant of AED in pregnancy. Frisium, used as a palliative care drug in most of the AED in pregnancy. Studies as received that lacosamide could be used as prophylactic drug in Anti-epileptic. Finally, levitiracetam proven to be the safest drug used as AED in pregnancy either alone or in combination with other drugs.

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