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The use of Valproic Acid in Pregnant Women in the Outpatient Clinic at Dr. Soetomo Hospital between 2017-2020 and the Side Effects that Arise in Babies Born

Heri Munajib [1,2,3], Wardah Rahmatul Islamiyah [2,3,4], J Eko Wahono [2,3]
[1]Neurology Resident, Faculty of Medicine, Universitas Airlangga
[2]Department of Neurology, Faculty of Medicine, Universitas Airlangga
[3]Dr. Soetomo General Hospital
[4]Universitas Airlangga General Hospital

Heri Munajib
Department of Neurology, Faculty of Medicine,
Universitas Airlangga, Surabaya, INDONESIA
Jalan Mayjen Prof. Dr. Moestopo 47, Surabaya, Indonesia

Abstract:-

Background: Valproic acid is commonly used in epilepsy patients, both focal and generalized epilepsy, in many cases, female epilepsy patients receiving valproic acid therapy are not easy to replace valproic acid therapy with other AEDs, therefore, when epilepsy patients are faced with a program pregnancy often treatment with valproic acid is unavoidable. The FDA's statement for pregnant women with valproic acid is category X. Based on this fact, how data and profiles of epilepsy patients in Indonesia are still rarely found. supplementation of high doses of folic acid and other minerals is very helpful in minimizing the teratogenic effects of valproic acid for infants for patients with epilepsy.

Objective: To report clinical and epidemiological the use of valproic acid in pregnant women in the outpatient clinic at DR. Soetomo Hospital between 2017-2020.

Methods: This is a retrospective study. All patients who were treated in outpatient care unit in January 2017-September 2020

Results: We obtained data from 2017-2020, 25 pregnant women with a history of epilepsy, data obtained 25 of them received valproic acid, 20 babies gave birth with live babies and 5 babies died, IUGR 8 babies, congenital malformations were found in 6 babies with 4 babies having congenital malformations from pregnant women with a history of epilepsy receiving valproic acid therapy.

Conclusion: Management Before Conception and supplementation of Folic acid 1 mg/day for epileptic patient during pregnancy can reduce the risk malformation congenital in the baby.

Keywords:- *Epileptic patient with pregnancy, DR Soetomo Hospital, Valproic acid, Folic acid.*

I. INTRODUCTION

People with epilepsy are estimated to be around 2 – 3% in the general population, of which half are women, and about 20 – 25% of all people with epilepsy are women of childbearing age (WUS)1,2. The prevalence of women with epilepsy in pregnancy is about 0.3 - 0.8 %3. Although most women with epilepsy with pregnancy give a good outcome, they are still exposed to the risk of seizures in the mother and the teratogenic effects of anti-epileptic drugs (OAE) on the fetus.4

Approximately 80% of women with epilepsy with pregnancy take at least 1 AED to control seizures.5 Epileptic women who were free of seizures during pregnancy were 66.6%, and 33.3% who had seizures, consisting of 15.2% generalized tonic clonic seizures (BUTK) and non-BUTK (18.2%).6 It is estimated that 3-7 babies out of every 1000 births are born to women with epilepsy.7 Most children (96%) of epileptic women who took OAE were born normal, without Major Congenital Malformation (MKM).8 The mean incidence of MHM in infants in the general population is around 1.6 – 3.2%, almost the same as the mean incidence of MHM in infants of epileptic women without OAE. The mean incidence of MHM in infants of epileptic women taking OAE is around 3.1 - 9%, about 2-3 times higher than the general population.9 Exposure to several AEDs during pregnancy, especially valproate, has adverse effects on the child's cognitive and behavior.10 Epileptic women who took valproate during pregnancy had children with 11-12 points lower Intelligence Quotient (IQ) compared to exposure to other AEDs,11 and had a 2.95 times higher risk of having children with autism (95% CI:1.42-6, 11) than epileptic women without OAE. 12

Understanding epilepsy in pregnancy is very important because its management is faced by two different individuals. A neurologist must know the physiological process of a pregnancy, the growth and development of the fetus in the womb, the factors that influence the occurrence

of seizures during pregnancy and the teratogenic effects of OAE in children. The interactions between epilepsy, OAE, mother and fetus should also be understood. If epilepsy in pregnancy is not understood, it will complicate the management of epilepsy in pregnancy and will harm both the mother and the fetus.13,14,15

Management of epilepsy in pregnancy aims to control seizures with minimal adverse effects on the mother and fetus, complicated by the lack of studies based on class 1 evidence, due to ethical concerns in research in pregnant women. The reason for making this paper aims to understand epilepsy in pregnancy, so that the management of epilepsy in pregnancy is better, can balance the risk of seizures and the teratogenicity of OAE as optimally as possible. Thus, the management of epilepsy in pregnancy is expected to get the best outcome for both mother and child.13,14,15.

II. PREGNANCY

A. Physiological Changes in Mother

Pregnancy is a condition in which anatomical and physiological changes occur, which are important to meet the increased metabolic needs during pregnancy, and to meet the needs of fetal development, so that the mother and fetus survive until delivery. Several physiological changes can affect the occurrence of seizures during pregnancy. Each pregnancy has its own form / pattern of seizures and cannot be predicted from previous pregnancy experiences.[13]

These anatomical and physiological changes can alter the pharmacokinetics of drugs.[16,17] Understanding the physiological changes during pregnancy is important for optimizing the management of epilepsy in pregnancy.[16] The following are some of the physiological changes in pregnancy.

a) Cerebrovascular Changes

One of the most important adaptations of the cerebral circulation during pregnancy is to counter the effects of circulating vasoactive factors. These vasoactive factors include a large number of hormones secreted from the placenta, ovaries, and brain in the maternal circulation, including pro- and anti-inflammatory cytokines, chemokines, steroids, and growth factors. These factors are indispensable for the development and safety of the fetus, as well as the adaptation of other organs to pregnancy. Arteries in the brain uniquely adapt during pregnancy to counter the increase in circulating vasoconstrictors, which usually occurs late in pregnancy. Plasma exposure from pregnant women causes posterior cerebral artery vasoconstriction in non pregnant rats, but this vaso constrictive effect does not appear in pregnant rats, this is due to development of resistance to circulating vasoconstrictors or increased sensitivity to vasodilators during pregnancy. Interestingly, this process is only specific to cerebral vasculature. The mechanism underlying the resistance of blood vessels in the brain to vasoconstrictor effects remains unclear, possibly involving receptor down regulation or changes in the endothelium that regulate vascular tone in response to plasma. Cerebral circulation adaptations are thought to prevent constriction in response to circulating factors, to maintain cerebrovascular resistance and physiological blood flow to the brain during pregnancy.[18]

Auto regulation of cerebral blood flow (ADO) is an intrinsic mechanism of the brain to maintain a relatively constant blood flow to the brain in response to changes in blood pressure. In healthy people who are not pregnant, the ADO curve is between 60-160 mmHg. During pregnancy, it is estimated that the ADO curve will shift/widen both the upper and lower limits. The effect of pregnancy on ADO auto regulation is protective, that is, it prepares the pregnant woman's brain to maintain blood flow in the face of hypotension and acute hypertension.[18] According to Chang et al, although there is a decrease in ADO (especially the middle cerebral artery on transcranial Doppler examination) there are no changes in cerebral auto regulation during pregnancy.[17]

b) Hematological Changes

During pregnancy the total body fluid increases by about 6.5 - 8 liters.[16,19] Blood volume increases gradually by 10 - 15% starting at 7 weeks of gestation and reaches a peak at 30 - 3416 weeks. Total blood volume increases by about 1,500 - 1,600 milliliters (ml), and plasma volume increases by 30 - 50%, or approx. 1,200 – 1,300 ml during pregnancy. This increase was greater in multi gravida than in primi gravida. In women who are pregnant with twins, the increase in plasma volume can reach 70%. This increased plasma volume causes a decrease in the peak level of the drug.[20]

Plasma protein concentration decreases with increasing gestational age, especially albumin (about 10 grams/liter)and glycoprotein acid. These plasma proteins are important as transporters of OAE in the blood circulation. A decrease in albumin levels causes a decrease in total levels and an increase in free drug levels.[15]

c) Cardiovascular Changes

Cardiovascular changes are very important to meet the oxygen needs of pregnant women and fetuses, as well as optimal nutrition for the fetus. In pregnancy there is an increase in blood volume, which will affect stroke volume. Stroke volume is the amount of blood pumped into the aorta each cycle, increasing by 20-30% during pregnancy. In pregnancy there is also an increase in heart rate starting from the beginning of pregnancy and reaching a peak and stable in the 3rd trimester. Cardiac output is the product of the stroke volume and heart rate. As a result of increased stroke volume and heart rate, cardiac output increases by 30-50% during pregnancy, starting at 6 weeks of gestation and then peaking and stabilizing in the middle of the third trimester.[16,17]

Increased cardiac output and systemic vasodilation result in increased blood flow to other organs such as the lungs, kidneys, uterus, breasts, and skin. .Blood flow to the uterus and placenta reaches 25% of cardiac output which is about 500 ml/min and is very important for fetal development. Maternal cardiovascular disorders associated with cyanosis, hypoxia or lower cardiac output, will reduce

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blood and oxygen flow to the fetus. This can increase the risk of fetal complications such as fetal growth restriction, miscarriage, and preterm delivery.[17]

d) Respiratory Changes

In pregnant women, there are several anatomical changes in the respiratory system, which causes a decrease in total lung capacity by 5%. Functional residual capacity decreased by 10-25%17,20. Functional residual capacity is the volume of air remaining in the lungs after a normal expiration. Oxygen consumption increased by 30%16,20. Increased oxygen consumption and reduced functional residual capacity cause pregnant women to have low oxygen reserves so that they are susceptible to hypoxia.[16,17]

e) Endocrine Changes

Estrogen levels increase gradually in the 1st and 2nd trimesters, and change only slightly in the 32nd trimester. The ratio of estrogen and progesterone increases to a peak between the 8th and 13th weeks. Estrogen can increase the activity of the glucuronidase enzyme in the liver.[16]

f) Changes in Kidney

Blood flow to the kidneys is increased and accounts for 20% of cardiac output. Blood flow and glomerular filtration increase by 50-80% during pregnancy. This increase process begins shortly after conception, continues in the 2nd trimester, then decreases at the end of pregnancy. The increased glomerular filtration rate will affect the clearance of drugs excreted in the kidney. Creatinine clearance increases by 25% until the 4th week and continues to rise to 45% by the 9th week of gestation. This increased creatinine clearance will increase the elimination of the drug excreted in the kidney by about 20 - 65%, so that its half-life is shortened. At the same time, there is an increase in the excretion of proteins and globulins. In the kidneys, sodium and water retention also occurs which results in an increase in plasma volume. [16,17,20]

g) Digestive Changes

The increase in progesterone during pregnancy results in decreased gastrointestinal motility and relaxation of the gastroesophageal sphincter, resulting in delayed gastric emptying and increased gastrointestinal transit time by 30-50%16,20. This is also accompanied by an increase in intra-abdominal pressure due to the growing uterine pressure, so that all of this results in emesis. Complaints of nausea and vomiting complained of 70% - 85% of pregnant women, and usually occurs in the 1st trimester. The exact cause is not fully understood, but it is possible that the hormone human chorionic gonadotropin (hCG) reaches peak levels in the 1st trimester and begins to decline in the 2nd trimester. In pregnant women with twins, higher hCG levels are found so that there is a greater risk of nausea and vomiting.[17]

h) Changes in Liver and fat

Enzymes that are important for drug metabolism, namely the cytochrome p 450 class and glucuronyl transferase, the activity of these enzymes increases during pregnancy. Fat reserves also increase so that the elimination of fat-soluble drugs decreases.[21]

III. FETAL DEVELOPMENT STAGE

The stages of fetal development are a special development in a certain time span and each stage has its own susceptibility to exposure to a substance.[19]

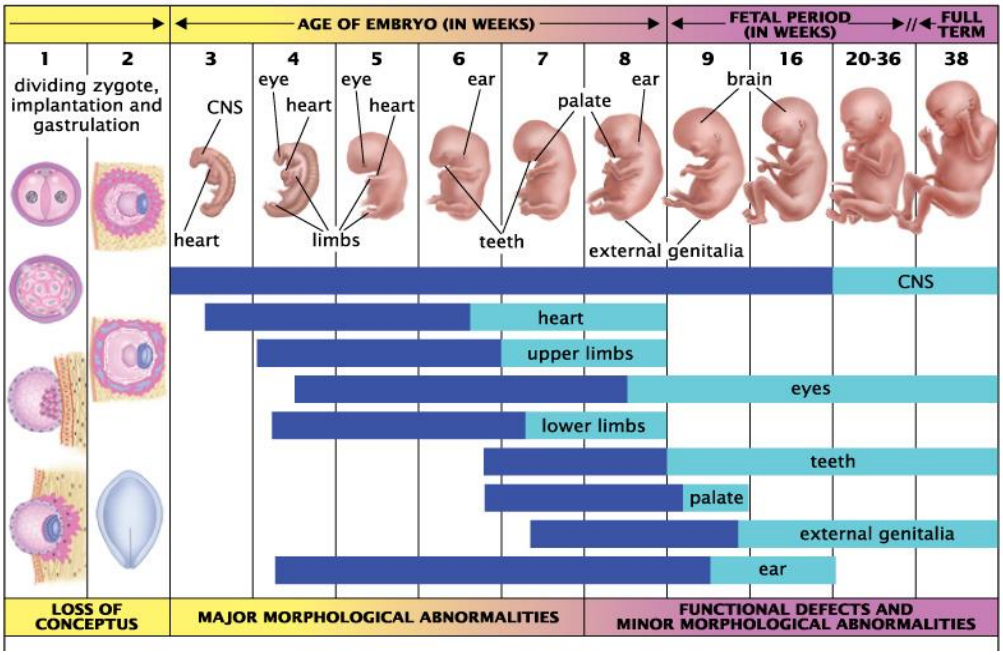

Fig. 1 : Stage of fetal development and risk of fetal abnormalities due to exposure at a certain time. [24]

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A. Epilepsy

a) Definition of Epilepsy

Epilepsy is a brain disease characterized by the following conditions/symptoms, namely: 1) There are at least 2 unprovoked seizures or 2 reflex seizures with a time interval between the first and second seizures of more than 24 hours; 2) One unprovoked seizure or 1 reflex seizure with the possibility of recurrent seizures in the next 10 years is the same as (minimum 60%), if there are 2 unprovoked/reflex seizures; 3) A diagnosis of epilepsy syndrome has been established. Reflex awakening is an arousal induced by specific triggering factors, namely certain sensory and cognitive stimuli. Certain sensory stimuli are visual, tactile/proprioceptive, sound, and music. Cognitive stimuli are praxis, reading, speaking. If the stimulus is repeated it will cause an awakening.[30,31,32,33,34]

Epilepsy was considered 'resolved' (no longer present), if the patient was past the age of the age-related syndrome or was seizure free for 10 years, with the last 5 years without OAE.[31]

b) Epilepsy Classification

The ILAE Classification of Epilepsy has been updated to reflect the attainment of an understanding of epilepsy and its underlying mechanisms, following the most recent scientific advances since the last classification in 1989. As an important tool for clinician practice, the classification of epilepsy must be relevant and dynamic to changes in thinking, yet powerful. and can be translated into all areas. Its primary purpose is for patient diagnosis, but it is also important for epilepsy research, development of antiepileptic therapy, and worldwide communication. The new classification stems from a draft document submitted for public comment in 2013, which has been revised to incorporate extensive feedback from the international epilepsy community including several repeated consultations.[35]

This new classification of epilepsy requires three steps, starting with the first step, namely, determining the type of seizure, according to the new definition and classification of seizures in 2017. The second step is the diagnosis of the type of epilepsy, including focal, generalized, or a combination of focal and generalized epilepsy. The third step is to determine the epilepsy syndrome. Epileptic syndromes can have several etiologies. The etiology is divided into six groups, namely structural, genetic, infectious, metabolic, immune, and unknown. New terminology was introduced such as developmental and epileptic encephalopathy. The terms benign were replaced by the terms self-limited and pharma coresponsive, as they were more appropriate. This new framework is expected to help improve epilepsy treatment and research in the 21th century.[36]

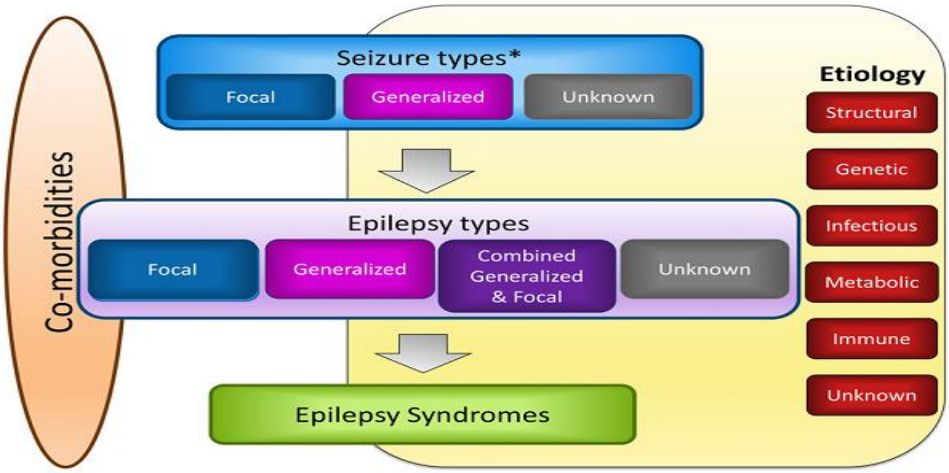

Fig. 2: Epilepsy Classification based on ILAE 2017.[36]

c) Epileptic seizure pathophysiology

The cerebral cortex generally consists of 2 neurons, namely projection/principle neurons and interneurons. Projection neurons (eg pyramidal neurons) project/send information to distant neurons and are primarily excitatory. In contrast, interneuron cells (eg basket cells) transmit local information and have primarily inhibitory functions. Interneuron cells play an important role for local inhibition, especially the formation of inhibitory feedback loops, when a projection neuron synapses on a local inhibitory neuron, where the synapse will return to the projection neuron. The basic response to neuronal stimulation is the creation of an action potential, with the spread of depolarization along the axon and the release of neurotransmitters at the axon terminal. In epileptic patients there is a hyperexcitatory state of neurons caused by increased excitation, decreased inhibition, changes in voltage-gated ion channels, or intra/extracellular changes leading to a more depolarizing state.[27]

The main inhibitory neurotransmitter is gamma-aminobutyric acid (GABA) and the excitatory neurotransmitter is glutamate. There are 2 glutamate receptors, namely ionotropic and metabotropic (related to membrane G proteins). The major ionotropic receptors of glutamate are -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainite, and N-methyl-D-aspartate (NMDA), all of which are permeable to sodium

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and potassium ions. NMDA receptors are also permeable to chloride ions mediated by magnesium ions and cause excitotoxicity due to excessive neuronal activity. The main GABA receptors are GABA-A which is located at the postsynaptic and GABA-B which is located at the presynaptic. Stimulation of the GABA-A receptor causes the membrane to be permeable to chloride ions, so that chloride ions enter the cell. The entry of chloride ions into the cell causes hyper polarization, makes the cell more stable, and it is more difficult to reach the threshold for depolarization and the formation of an action potential.[27]

At the cellular level, seizures are characterized by hyperexcitability and hypersynchronicity of neurons. Hyperexcitability is the increased response of a neuron to stimulation, and multiple, rather than single, action potentials may occur in response to a synaptic input. Hyper synchronization is the increased firing of neurons in a small or large area of the cortex, and the firing of these cells occurs in close time and distance. Hyper synchronization is characterized by increased excitability of surrounding neurons. The pathophysiology underlying the hyperexcitability of neurons are: 1) Changes in cell membrane function, namely increased cell membrane permeability; 2) Decreased inhibitory neurotransmission mainly by GABA-A or increased excitatory neurotransmission of glutamate; 3) Changes in the number, balance, sensitivity or function of receptors, eg GABA-A or glutamate receptors; 4) Changes in the concentration of extracellular ions such as potassium or calcium.[28,29]

When discharge occurs, synchronization with other neurons will occur and spread to the surrounding brain area. Under normal conditions the spread of discharge can be prevented/inhibited by an inhibitory neuron in the vicinity. However the activation of the surrounding neurons is greater than the inhibition. The recruitment mechanism in hypersynchronous, including repeated discharges results in: 1) Increased extracellular potassium ions thereby depolarizing the surrounding neurons; 2) Accumulation of calcium ions in the presynaptic will increase the release of glutamate; 3) Depolarization induced by NMDA receptor activation causes an influx of calcium ions and subsequent neuronal activation. Glial cells play an important role as a buffer to regulate the balance, namely the uptake of potassium and glutamate ions, changes in the function of glial cells can cause hyperexcitability.[28,29]

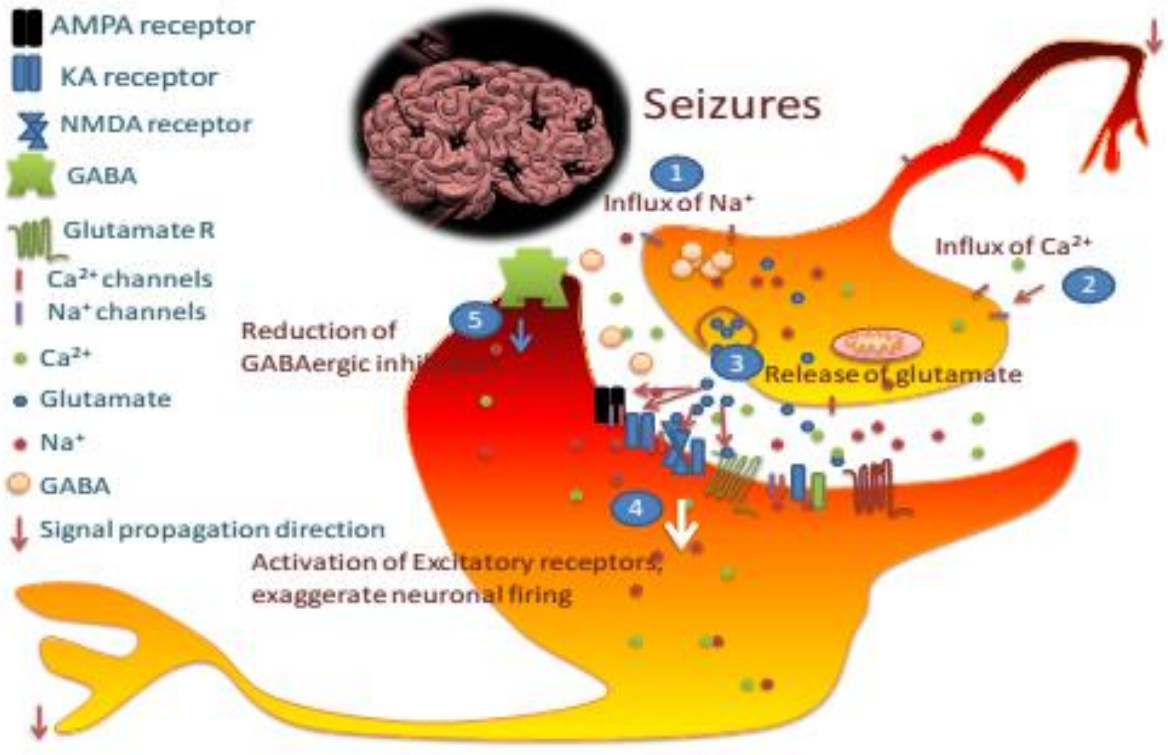

Fig. 3 : Neuronal firing

Picture 3 : Neuronal firing. Neuronal firing is triggered by changes in signal propagation, which can be caused by abnormalities in the stability of the neuronal membrane or the connections between neurons. The epileptic burst consists of sodium (1) and calcium (2) dependent action potentials. The opening of voltage channels activated by calcium ions causes an increase in the neurotransmitter (glutamate) in the synaptic cleft (3). Increased glutamate activates NMDA, AMPA and kainate receptors, leading to an influx of sodium and calcium ions into cells through gated channels, resulting in neuronal hyperexcitability (4). Increased uncontrolled disinhibition is one of the keys to epileptic seizures, because decreased inhibition by

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GABAergic causes synchronized burst discharge of a group of cells (5).[30]

B. Epileptic seizures during pregnancy

a) Frequency and Time of Epileptic seizures During Pregnancy

The frequency of seizures during pregnancy varies and is difficult to predict. In the European Registry of Antiepileptic Drugs and Pregnancy (EURAP) study involving 3,806 pregnancies, seizure information was obtained in 3,735 pregnancies. When the 2nd and 3rd trimesters were compared with the 1st trimester, as many as 2,634 (70.5%) seizure frequency did not change, of which 2,521 (95.7%) were seizure free and 1,037 experienced a change in seizure frequency during pregnancy. Of those who experienced a change in seizure frequency, 448 pregnancies (12%) experienced a decrease in seizure frequency in the 2nd and 3rd trimesters or both, 589 pregnancies (15.8%) experienced worsening of seizures. A total of 64 subjects (1.7%), the frequency of seizures was categorized as increasing or decreasing in the 2nd and 3rd trimesters compared to the 1st trimester.[6,36,37,38,39]

b) Factors Affecting the Occurrence of Seizure during Pregnancy

Brodkotorb & Reimers divides the factors that influence the occurrence of seizures during pregnancy including behavioral, physical, pharmacokinetic, and natural factors.[40]

BEHAVIORAL FACTORS	Emotions (positive/negative) Psychosocial problems Lack of sleep Fear of seizures, especially during childbirth Worried about breastfeeding Misconceptions about inherited diseases Non-adherence to taking medication
PHYSICAL CHANGE	nauseous vomit pelvic fatigue/distortion frequent awakenings/leg cramps changes in hormone levels
CHANGES IN THE PHARMACOKINETICS OF OAE	reduced drug absorption increased distribution volume increased protein changes increased metabolism increased renal clearance
NATURAL FLUCTUATIONS IN GENERATION FREQUENCY	

Table 1 : Factors that influence the occurrence of seizures during pregnancy. [40]

c) The Effect of Seizure on Pregnancy

Most studies in epileptic women with pregnancy have involved treatment with AEDs, so the side effects of OAEs could be a confounding variable. The effect of seizure type on pregnancy is relatively difficult to determine. The fetus in the womb is not easily accessible by scientific research, therefore, the immediate effect after the seizure is difficult to determine. Despite these obstacles, the types of focal seizures generally have minimal effect on the fetus, the effect of focal seizures without disturbance of consciousness has no effect on pregnancy, whereas focal seizures with impaired consciousness can result in trauma, and the mother is unable to perform a normal delivery. There were 2 case reports about the effect of complex partial seizures, causing bradycardia to the fetus, but the fetus was born healthy.[41,41,43,44,45]

d) Effect of General Awakening on the Fetus

In BUTK there are changes in electrolytes, oxygenation, and blood pressure that can harm fetal development. The immature fetal brain is particularly susceptible to these changes. BUTK is associated with fetal intracranial hemorrhage, hypoxia and fetal death, but this is not due to convulsive activity, but to physiological changes in the mother during seizures. BUTK causes hypoxia and lactic acidosis, these biochemical changes will be transferred to the fetus through the placenta. Decreased placental blood flow, uterine contractions, lactic acidosis and post ictal apnea are possible causes of fetal hypoxia and decreased fetal heart rate. Fetal hypoxia due to this seizure can cause organ damage and if prolonged can cause fetal death. [46,47,48,49,50]

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Category	Brief description	FDA pregnancy category definition
A	Proven no risk to humans	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities
B	No evidence of risk to humans	Animal studies have revealed no evidence of harm to the fetus, however, there are no adequate and well-controlled studies in pregnant women or Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus
C	Risks cannot be ruled out in humans	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women or No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women
D	Clear evidence of risk in humans	Adequate well-controlled or observational studies in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk
X	Contraindicated in human pregnancy	Adequate well-controlled or observational studies in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant

Table 2 : Anti-epileptic drugs in pregnancy, FDA definition of drug category in pregnancy. [58]

Number	Oral Anti Epileptic	FDA Category
1.	*Acetazolamide, brivaracetam, clobazam, eslicarbazepine acetate, ezogabine/ retigabine, felbamate, gabapentin, lacosamide, lamotrigine (immediate release), levetiracetam, oxcarbazepine, perampanel, pregabalin, rufinamide, tiagabine, vigabatrine, zonisamide*	C
2.	*Carbamazepine, clonazepam, diazepam, lamotrigine (extended release), lorazepam, phenbarbital, phenytoin, topiramate*	D
3.	*Valproate*	X
4.	*Ethosuximide,methsuximide, primidone*	not yet formally categorized

Table 3 : Anti-epileptic drugs in pregnancy, FDA definition of drug category in pregnancy.[58]

e) Effect of Anti-Epilepsy Drugs on Pregnancy

Treatment with OAE results in seizure-free or reduced seizure frequency in 60-70% of patients. Long-term administration of OAE is still the mainstay of epilepsy therapy. Patients need to be explained about long-term treatment to comply, and about the possible side effects of OAEs. [59,60,61]

OAE	Minor Side Effects	Life-threatening side effects
Carbamazepine	rash, sedation, headache, ataxia, nystagmus, diplopia, tremor, impotence, hyponatremia, agranulocytosis, leukopenia, thrombocytopenia, hyponatremia, weight gain	Anticonvulsant hypersensitivity syndrome (AHS), Steven-Johnson syndrome (SJS), liver failure, hematology (aplastic anemia)
Clobazam & Clonazepam	Severe sedation, fatigue, drowsiness, cognitive and behavioral disturbances, restlessness, impaired coordination, withdrawal syndrome	No side effects
Gabapentine	Weight gain, peripheral edema, behavioral changes, impotence	acute pancreatitis, hepatitis, acute renal failure
Lacosamide	Dizziness, diplopia, rash (rare)	No side effects
Lamotrigine	rash, insomnia, dizziness, diplopia, headache, ataxia, asthenia, blurred vision, may trigger myoclonic seizures, thrombocytopenia	AHS, liver failure, haematological disorders, SJS
Levetiracetam	Agitation, behavioral and psychotic changes, asthenia, dizziness, somnolence, headache, thrombocytopenia, leukopenia	Unknown
Oxcarbazepine	rash, headache, dizziness, nausea, somnolence, ataxia, diplopia, hyponatraemia	AHS, haematological disorders
Phenobarbital	rash, drowsiness, impaired cognitive and concentration, hyperkinesia and agitation in children	AHS, haematological disorders (aplastic anemia), hepatotoxicity, connective tissue and bone marrow disorders, SJS
Phenytoin	rash, ataxia, drowsiness, gum hypertrophy, hirsutism, anorexia, nausea, agranulocytosis, thrombocytopenia, decreased intestinal calcium absorption	AHS, liver failure, haematological disorders (aplastic anemia), SJS
Pregabalinee	Weight gain, myoclonus, dizziness, somnolence, ataxia, confusion	Kidney failure, congestive heart failure
Topiramate	Somnolence, anorexia, fatigue, attention/concentration difficulties, memory impairment, psychomotor slowing, metabolic acidosis, weight loss, language disorders, kidney stones, glaucoma	Liver failure, anhidrosis
Valproate	Nausea, vomiting, dyspepsia, weight gain, constipation, hair loss, tremor, amenorrhea, Polycystic Ovarian Syndrome, alopecia in women	liver and pancreas failure
Zonisamide	Drowsiness, anorexia, irritability, photosensitivity, weight loss, kidney stones	AHS, anhidrosis, aplastic anemia

Table 4 : Side effects and Life-threatening Side Effects of OAE. [60,61]

f) Effects of Anti-Epilepsy Drugs on Children

a. Teratogenic Effects of Anti-Epilepsy Drugs

Teratogenicity is the occurrence of adverse effects in developing organisms, resulting from exposure to chemicals before conception, during prenatal and postnatal development, and acquired at any time in the organism's age range. The main manifestations are structural abnormalities, functional deficiencies, changes/impaired growth and death of the organism.[61,62,63,64]

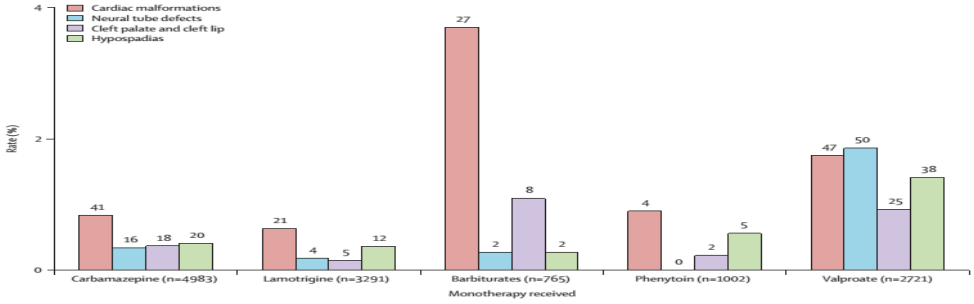

Fig. 4 : The incidence of specific MHM due to exposure to certain AEDs asmonotherapy.[65]

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b. Functional Deficiency/Functional Teratogenesis (Neurodevelopment/Cognitive and Behavioral)

Functional deficiency/functional teratogenesis: dysfunction/disease without malformations/structural abnormalities that may not be present at birth, eg low IQ. Neurodevelopment, neurobehavioral, intelligence and cognitive development are terms that are used interchangeably to refer to the functional output of the brain ranging from motor performance, intelligence, speed of information processing, social function, and other cognitive skills.[51,64,65]

From the results of the review showed, exposure to valproate at a dose of 800-1000 mg/day was more at risk of having children with lower IQs than other OAEs, and lower IQs with increasing doses46. According to the American Academy of Neurology (AAN), the cognitive outcomes of exposure to polytherapy may be lower than exposure to monotherapy, but the magnitude of the risk of various combinations of OAEs is unknown.

Children of epileptic women who were exposed to valproate during pregnancy had a 2.9 times greater risk of developing autism (95% CI: 1.4 - 6) than those who were not exposed to valproate. Valproate exposure during pregnancy, increased the risk of children suffering from Attention Deficit Hyperactivity Disorder (ADHD) compared to the general population (21.4% and 7% p = 0.003).[66,67]

c. Organism Death

Organismal death is death in utero or neonatal unrelated to malformation. Based on the EURAP study, intrauterine deaths were found, namely spontaneous abortion of 592 (8.4%) and stillbirth of 40 (0.6%). There was no difference in the risk of spontaneous abortion (p = 0.5) and stillbirth (p = 0, 97), between epileptic women taking and without OAE and between exposure to monotherapy and polytherapy (p=0.5 and p=0.65). Meanwhile, in other literature, the risk of intrauterine death (spontaneous abortion and stillbirth) increases with exposure to polytherapy (95% CI, RR: 1.38: 1.14–1.66). There was no difference in the mean incidence of intrauterine death between various exposures to AED monotherapy (8.2%; 95% CI: 7.5%–8.,9%). [51,52,64]

IV. METHODS

This is a retrospective and record-based study. The patients were identified from the medical records, starting from January 2017 to September 2020.The inclusion criteria of our study was patients with pregnant women with a history of epilepsy and received valproic acid. Consent was sought for accessing the medical records. Patients who incomplete medical records were excluded. The following information was noted such as the demo graphic patient characteristics (age and sex) and clinical presentation (unilateral or bilateral). All data were analyzedusing SPSS 25.

V. RESULT

Between 2017-2020 at RSUD Dr. Soetomo, 25 pregnant women with a history of epilepsy, data obtained 25 of them received valproic acid, 20 babies gave birth with live babies and 5 babies died, IUGR 8 babies, congenital malformations were found in 6 babies with 4 babies having congenital malformations from pregnant women with a history of epilepsy receiving valproic acid therapy.

VI. CONCLUSION

Supplementation of folic acid 1-4 mg daily in cases of pregnancy with epilepsy who received valproic acid therapy can reduce the risk of congenital malformations in infants, this can be supported by management before conception to provide a low outcome rate on the incidence of teratogenic effects of valproic acid.

VII. DISCUSSION

To improve outcomes for women with epilepsy in pregnancy requires an individualized approach, with a team consisting of neurologists, obstetricians, general practitioners, nurses, and clinical pharmacists, with knowledge of the various aspects of epilepsy with pregnancy.

A. Management Before Conception

Management of women with epilepsy in pregnancy should ideally be carried out before pregnancy, so that a complete evaluation and thorough follow-up can be carried out, to determine the cause and severity of the disease. A complete medical history includes since when suffering from epilepsy, frequency of seizures, OAE used, type of epilepsy, and response to treatment. Previous pregnancy history, including maternal and infant outcomes, especially congenital abnormalities in previous children should also be considered7. Where possible their diagnosis and treatment are reviewed by a preconception epilepsy specialist, in order to optimize controlled seizures and rational treatment of OAEs before conception (level C)86. Management before conception includes the following stages.[58]

B. Administration of Folic Acid

Women with epilepsy planning a pregnancy or in the 1st trimester should be given folic acid to reduce the risk of MHM (level C). Sufficient data have not been obtained to determine folic acid dosage guidelines. All women taking OAEs should be offered folic acid 5 mg/day as much as possible before becoming pregnant. Most experts recommend giving high doses of folic acid 5 mg/day (10 x prophylactic dose) 1 month before conception until at least the first trimester.[65,66,67]

All women with epilepsy were given folic acid 5 mg until at least the first trimester of pregnancy to reduce the risk of MKM88. Women with epilepsy without OAE were given folic acid at a dose of 400 micrograms/day (level A). Folic acid dose 5mg/day given to: 1) women with epilepsy who are taking OAEs (level D); 2) women with epilepsy without OAE, who have a family history or previous child

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with neural tube defects (level A); 3) women with epilepsy without OAE but have a BMI > 30 (level A).[68,69]

Administration of folic acid 5 mg/day before conception may reduce the risk of cognitive impairment (level C). Epileptic women taking valproate should be given folic acid, which may reduce the risk of spontaneous abortion (level D).[70]

C. Selection, Replacement and Termination of OAE

Management of OAE before conception includes:

- Selection of OAE. The OAE chosen was the OAE that best suited the patient's characteristics (level B)88,89, namely based on the type of seizure and epilepsy syndrome.[60]
- Avoid valproate and poly therapy. Exposure to valproate and poly therapy should be minimized, where possible, changing medication prior to conception, considering switching to another appropriate AED and on the recommendation of an epilepsy specialist, after careful evaluation of the potential risks and benefits.
- Give the smallest effective dose for each OAE (level B).[71,72]
- Consider discontinuing OAE. Consideration of OAE is discontinued if it is free of seizures for 2 - 3 years86. If possible, the OAE can be discontinued or the lowest effective dose used and controlled seizures are expected 6 months before conception.

D. OAE Level Check

If OAE treatment is required during pregnancy, a range of therapeutic levels is required before conception91. Pre-conception reference levels of lamotrigine are determined after estrogen-containing oral contraceptives are discontinued and the dose of lamotrigine is reduced by 50-75%.[72]

E. Malformation Screening

Examination of alpha-fetoprotein levels was carried out at 14-20 weeks of gestation91. Detailed assessment of fetal anatomy by ultrasonography to detect structural congenital abnormalities of the fetus should be offered to all pregnant women with epilepsy at 18-20 weeks gestation (level D).[73]

F. Administration of Vitamin K

If the mother is taking enzyme-inducing AEDs, consider antenatal prophylaxis with oral vitamin K 20 mg daily in the last 4 weeks of pregnancy. If vitamin K is not given antenatally, then vitamin K 10 mg is given by slow intravenous injection over 10 minutes at the time of delivery or preterm delivery. There is insufficient evidence to recommend routine use of oral vitamin K in women with epilepsy taking enzyme-inducing AEDs to prevent bleeding in newborns (level D). There is insufficient evidence to recommend giving vitamin K to women with epilepsy to prevent postpartum hemorrhage. If there are additional risk factors for bleeding in the newborn (eg maternal liver disease, anticipated preterm delivery) consider giving the mother oral vitamin K (phytomenadione 10 mg/day) in the third trimester of pregnancy (level D).[74,75]

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