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Management of Pregnancy with Epilepsy: A Case Report

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Abstract: ***Epilepsy in pregnancy is a rare case with an incidence range between 0.5-1.0%. No antiepileptic medications are safe for pregnancy. Phenytoin use in pregnancy is associated with a 5-11% incidence of fetal hydantoin syndrome. Decision whether to continue or stop using phenytoin in pregnant women with epilepsy can be problematic. In this case report, we would discuss the management of a 34 year old multigravida who was known to have generalized epilepsy since 4 years earlier and on regular phenytoin use. During her pregnancy, she never had an episode of epileptic seizure and continued taking phenytoin and folic acid. Fetal scanning and regular phenytoin level monitoring were unremarkable. She finally gave birth to a normal 3100 gram vigorous male baby through spontaneous vaginal delivery. She continued the use of phenytoin during postpartum period and use IUD for contraception.***

Keywords: pregnancy, seizure, epilepsy, phenytoin, contraception

1. Introduction

Epilepsy is a chronic neurologic condition of repeated seizure that occurs without systemic provocation or neurologic disorder. Seizure is produced from abnormal abrupt change in a group of cerebral neurons. The most important diagnostic tool to establish epilepsy is the history of seizure such as whether there is an aura, description of seizure, period of seizure, history of febrile seizure during childhood, central nervous system infection such as meningitis, history of head injury with a decreased consciousness and family history of seizure[1]. About 40% of 18 million women with epilepsy in the world are on reproductive age group[2]. Prevalence rate of epilepsy on pregnancy is about 0.5-1%[3]. Wehereas, in Indonesia, there is no exact data regarding incidence rate of epilepsy in pregnancy.

Women with epilepsy are at increased risk of suffering from complications during pregnancy and delivery, such as spontaneous abortion, gestational hypertension, antepartum bleeding, and postpartum hemorrhage, compared to that of general population. Epilepsy also increase the incidence of intrauterine fetal death, premature delivery, intrauterine growth retardation, microcephaly, and major congenital amomalies.[2] Epilepsy is not a contraindication of pregnancy. More than 95% of pregnant women with epilepsy deliver healthy babies although they are on medication.[4] However, there is no antiepileptic drug (AED) considered to be safe on pregnancy. Major congential malfomations increase 2-3 times in babies and mothers who receive monotherapy antiepileptic drug. There is higher teratogenicity effect in mothers using valproic acid and polytherapy.[5]It is very important to reasses women with epilepsy regarding the possibility of newborn babies, focus on optimalization of antiepileptic drug, folic acid supplementation, and contraception to prevent unwanted pregnancy and minimalize complication risk.

Pregnancy is associated with changes in the metabolic hormones and antiepileptic drugs. Both of those things will influence the frequency of seizure. Hormones that has an influence on seizure attack in pregnant women are estrogen and progesterone.[6] In pregnant women, blood estrogen level will decrease so that it will excite the activity of glutamate decarboxylase enzyme and therefore the synthesis of gamma amino butyric acid (GABA) in brains will be decreased. This decrease in the concentration of brain GABA will excite the epileptic seizure.[7]

Pregnant women with epilepsy are faced with a unique condition. To stop using antiepileptic drug is not a realistic decision. Pregnancy increases the risk of seizure attack. Meanwhile, consumption of antiepileptic drug generally has teratogenic effect. Women with epilepsy who take the drug routinely before pregnancy, who continue to take the drug during pregnancy until spontaneous delivery of the healthy babies without congenital anomaly and the lack of data regarding epilepsy and pregnancy in Bali attract our interest to take this issue as a case report. We try to discuss and deepen the aspect of epilepsy toward pregnancy, pregnancy toward epilepsy, antiepileptic drugs toward congenital anomaly, and antiepileptic drug toward reproductive function of women. We hope this case report can be a reference or consideration in the management of the same case.

2. Case Report

A 34 years old multigravida came to Obstetric Emergency Unit of Sanglah Hospital, Denpasar, Bali,complaining watery vaginal discharge. She was diagnosed with G4P1021, 38 weeks and 3 days of gestation, singleton live pregnancy, poor obstetric history, secondary primigravida, premature rupture of membrane, and follow up of idiopathic epilepsy. Fetal weight was estimated to be 2838 grams. She had a history of generalized seizure since 2004 and the last episode of seizure was in 2013.She was not routinely taking her antiepileptic drug and forgot the name of the drug. Patient came for the first time on 11th July 2013 to Neurology Outpatient Clinic of Sanglah Hospital and started taking medication of phenytoin sodium 100 mg three times daily and folic acid 1 mg twice daily. During pregnancy, she never had an episode of seizure attack. Currently patient is

in the medication and routinely visit obstetric and neurologic clinics of Sanglah Hospital. Patient came at 5th August 2017 by bringing laboratory result with the phenytoin level in the blood of 3.64 ug/ml, in which the previous 3 months's level was 7.81 ug/ml. The last patient's EEG examination was at 5th September 2015 with the normal result and the diagnosis of idiopathic epilepsy with pregnancy and the therapy of epilepsy was to be continued.

She delivered the baby spontaneously with the occiput presentation. The baby was a male, cried spontaneously with the weight of 3100 grams. There were no congenital anomalies. The condition of the mother at post partum period was good with continued antiepileptic therapy. Patient subsequently used IUD as the method of contraception, this IUD was inserted at obstetric clinic of Sanglah Hospital, at 42 days post partum. Electroencephalograpy was performed after 3 years of seizure free and by continuing antiepiletic drug at neurologic clinic of Sanglah Hopsital. The result of EEG was normal, and therefore the dose of antiepileptic drug was decreased gradually.

3. Discussion

Epilepsy is aneurologic condition that can occur during pregnancy with the incidence rate of 0.5-1%.[3] There is no prohibition to epileptic patient to be pregnant. It is reported only 46% of women with epilepsy required repeated information about interaction between antiepileptic drug and contraception, 63% required pregnancy planning, and only 56% required folic acid supplementation.[4]Epilepsy in pregnancy can cause serious maternal and fetal complications.[8] Maternal complications that can occur are repeated seizure (hypoxia), status epilepticus, seizure during delivery, gestational hypertension, dan preterm delivery. During pregnancy, the patient in this case never suffered from seizure (repeated seizure), status epilepticus, or seizure during delivery. From the physical examination during antenatal visit, there was no increased blood pressure and during delivery there was normal blood pressure of 110/70 mmHg and therefore the gestational hypertension can be excluded. Other complication such as preterm delivery did not occur in this patient because when she came to emergency unit of Sanglah Hospital at September 24 2015 the gestational age was 38 weeks and 3 days (aterm).

Fetal complications that can occur due to epilepsy are abortion (two times more frequent than normal), congenital anomaly (2-3 times more frequent than normal), hypoxia, lack of gestational age and low birth weight, premature delivery, smaller head circumference, low IQ, and abnormal attitude. The pregnancy in this patient is the fourth pregnancy with one history of abortion at 2004. But, based on patient confession, the abortion occured before the first seizure attacked patient at 2004. The male baby was delivered with the weight of 3100 grams and cried spontaneously, and therefore, the complications such as low birthweight and premature delivery were not found in this patient.

The accuracy of diagnosis is the basic of therapy, the less precise diagnosis can cause inadequate therapy. The primary aim of therapy of epilepsy is in effort to make epileptic patient to have a normal life and achieve an optimal quality of life accordant to disease course and physical or mental disability. The hope of the therapy is "free of seizure without adverse effects". Therapy in epilepsy can be pharmacologic therapy and non-pharmacologic therapy. In pharmacologic therapy, antiepileptic drug is given if the diagnosis of epilepsy is established, there are minimum of 2 seizure within one year, patient and or his/her family have received explanation about aim of therapy and possible adverse effects caused by antiepileptic drug, repeated seizure although the precipitating event has been avoided (e.g. alcohol, lack of sleeo, stress). The drug is started with monotherapy, using preferred AED according to type of seizure and type of epileptic syndrome, started from low dose and increased until the effective dose is achieved or the appearance of side effect.[9-10]

In this case, patient took antiepileptic drug phenytoin with the dose of 100 mg three times a day and folic acid 1 mg two times a day before pregnancy and continued during pregnancy until after delivery. Phenytoin as antiseizure drug is based on seizure type and type of epileptic syndrome. Antiepileptic drug for the patient with general type of seizure and tonic-clonic seizure is phenytoin and carbamazepine.[11] The choice of phenytoin as the first line antiepileptic drug is because that phenytoin is effective as monotherapy for general seizure, its low starting dose of phenytoin and everyday dose (200-300 mg/day) and the level of plasma drug that can be measured by blood laboratory. The latter property of drug allows the monitoring and drug effectivity to be known if there is any repeated seizure due to insufficient dose of therapy or if there is adverse effect due to high plasma drug level.

About 5-11% fetal hyndantoin syndrome occurs due to consumption of phenytoin, they are craniofacial anomaly, fingernail hypoplasia, growth and development disturbance, heart defect, and cleft palate,[12] whereas the International Registry of Antiepileptic Drugs and Pregnancy (EURAP) in the journal of *Teratogenic effects of antiepileptic drugs*, *Lancet Neurol* 2012 (Table 1) found that the occurence of major congenital malformation due to phenytoin was not different to that of carbamazepine medication, that is about 6%. The definition of major congenital anomaly in general are structural abnormality in term of medic, functional, or cosmetic. Structural anomaly occurs during organogenesis, at 8-10 weeks of gestational age. Therefore, it is recommended to give folic acid supplementation for the women planning to be pregnant and during pregnancy particularly in the first trimester with the dose of 1-5 mg per day to prevent folic acid deficiency so that the malformation or neural tube defect due to phenytoin do not occur. It was found that mean IQ is higher in the children receiving preconceptional folic acid compared to that of children who did not receive folic acid.[13]

It is estimated that in about 30-50% pregnant women there is increased seizure. In about 20-33% pregnant women with epilepsy there will be increased seizure frequency, there will be decreased frequency in 7-25% patients and there is no significant change in 50-83% patients.[14] Physiologic change and psychosocial adaptation during pregnancy can alter

frequency of seizure such as alteration in hormonal concentration, change in metabolism of antiepileptic drug, sleep disturbance, and stress.Seizure can be worsen during pregnancy, not only associated with hormonal change but also due to that most of pregnant women stop their own medication by themselves because of concern regarding occurence of abnormality on fetus.[15]

Pregnancy is associated with alteration in the metabolism of hormones and antiepileptic drugs. Both of those things will influence the frequency of seizure. Hormones which have influences on seizure attack in pregnant women are estrogen and progesterone. In pregnant women the blood estrogen level is decreased therefore the activity of glutamate acid decarboxylase enzyme will be excited and because of that, the synthesis of gamma amino butyric acid (GABA) in the brain will be decreased. With the decreased concentration of GABA in the brain, the epileptic seizure will be excited. The physiologic alteration during pregnancy will cause hemodilution. Because of decreased glomerolus filtration will cause fluid retention and so edema, the level of drug in the plasma will subsequently be decreased. The fluid retention will cause hyponatremia. This condition will produce partial disturbance of natrium pump that causes increased neuronal excitability dan precipitates seizure.[6,7]

In this patient during pregnancy, there was no seizure. The risk of repeated seizure is very low if there are no abnormalities in the physical and neurological examinations, and normal EEG and neuroimaging findings.[16]Mothers who had free seizure during minimum 9 months before pregnancy, and found that the majority (84-92%) will still be seizure free during their pregnancy.This result is in accordance with study by Mawer et al. at 2010 who suggested that part of women with epilepsy (52%) would not suffer from seizure during pregnancy.[17] Also, in this patients, during delivery and post partum period, there was no seizure. This can be caused by the concentration of antiepileptic drug, i.e. phenytoin, in patients' blood is in sufficient theurapeutical dose. Beside that, factors which can cause increased seizure such as sleep disturbance, anxiety, hyperventilation during pregnancy can be prevented.

Vaginal delivery is the prefered method of delivery for mothers with epilepsy. If patients suffer from seizure due to delivery pain, cesarean section can be considered after the condition is stabilized. Tonic-clonic seizure occurs during delivery process or after delivery in 1-2% mothers with epilepsy. Seizure during delivery can cause temporary fetal bradycardia. Fetal heart rate must be resuscitated. If the fetal bradycardia persists, fetal distress or placental solution should be considered and cesarean section must be performed. Therefore, delivery must be conducted in a hospital which has facilities to care for epileptic patients and intensive care unit for neonates.

This patient delivered male baby spontaneously, with the weight of 3100 grams, immediate crying, and gestational age of 38 weeks without congenital anomalies. About 90% women with epilepsy will deliver healthy babies with aterm gestational age.[1]Epileptic women who take antiepileptic drug regularly will not have a significant increased rate of cesarean section.[16]During delivery, antiepileptic drug must be continued. Not all of antiseizure drugs are available in intravenous form. Phenytoin and levetiracetam are available in intravenous form. The treatment of seizure during delivery process can be diazepam 10 mg administered intravenously or phenytoin 15-20 mg/kg bodyweight/ day given in divided dose twice a day.[5]In this case, patient continued antiepileptic drug phenytoin with the dose of 100 mg three times a day, with the last consumption was before patient was admitted to the hospital, and during delivery there was no seizure attack.

In the newborn babies of epileptic mothers, some experts recommend supplementation of vitamin K to decrease the risk of bleeding complication, nevertheless, there is no data from American Academy of Neurology which supports prenatal vitamin K supplementation. Newborn babies which were exposed by antiepileptic drug during intrauterine life were received vitamin K during delivery as a routine practice for all newborn babies.[12] The same thing was performed in this patient. This male baby was injected with vitamin K with the dose of 1 mg intramuscularly in order to decrease the risk of neonatal bleeding during delivery in a mother using antiepileptic drug.

Postpartum mothers keep breastfeeding their babies until reach the age of six months. Breasfeeding is not a contraindication to breastfeed in woman with antiseizure medication, in this case epilepsy is included. Valproic acid, phenobarbital, phenytoin, and carbamazepine are not transmitted into the breastmilk in clinically significant amount, it is different with second and third generation of antiepileptic drugs such as levetiracetam, gabapentin, lamotrigine, and topiramate.[16]Anyway, all antiepileptic drugs can pass into breastmilk. The level of concentration is varied from 18% until 79% of plasma level. Plasma concentration of antiepileptic drug on babies is not only determined by amount of drug on breastmilk, but also by not fully developed liver function and slower drug elimination. Newborn babies are monitored for sedative side effect during breastfeeding in mother with antiepileptic drug, in which the drug is loosely bound to protein. Total amount of drug transferred through breastmilk to the babies is far lower compared to that of the amount transferred through placenta during pregnancy.[1,18]

There are a lot of contraception choices for epileptic women. Hormone-based oral contraceptions are the most common contraception used to prevent pregnancy. This contraception is usually composed of estrogen and progesterone and therefore we call it as combination pill. Other choices are injection, implant planted under the skin, intrauterine device (IUD) or barrier method using condom.[16]There is no strong proof that contraception pill is associated withthe worsening of seizrue condition in epileptic women taking hormonal contraception. Antiepileptic drugs have a prime aim to control seizure. But, there are many factors to choose between antiepileptic drug therapy and hormonal contraception since some antiepileptic drugs can decrease the effectivity of contraception via pharmakokinetic interaction (Table 2). Estrogen and progesterone are metabolized by cytochrome P450 3A4. Phenobarbital, primidone, phenytoin, carbamazepine, and topiramate which are antiepileptic drugs, work on p450 microsomal isoenzyme

CYP3A4 which has a respnse to estrogen and progesterone metabolism (in which estrogen and progesterone are the components of contraceptive pills). This will yield increased metabolsime of combination contraceotive pill and therefore can cause contraception failure.

Valproic acid and new generation of antiepileptic drugs such as gabapentin, levetiracetam, and zonisamide do not influence liver enzyme and therefore do not influence the action of oral contraception pill. Contraception pill also can decrease antiepileptic drugs concentration such as lamotrigine dan therefore can cause increased risk of seizure. If oral contraception will be used, antiepileptic drug which increases microsomal enzymes should not be used.[19,20]Medroxyprogesterone injection may be effective in women with epilepsy. Depo-Provera is reported to be able to decrease seizure particularly in women with catamenial seizure. This injection is advised to be repeated every 10 weeks, different from the usual 12 weeks, due to theoretically such antiepileptic drug can decrease Depo-Provera effectivity.[21]

Beside pills that contain hormones, there are lot of contraception choices. Contraception method that does not influenced by enzyme from epileptic medications are levonogestrel IUS (Mirena) with the failure rate of 0.1%; DMPA (Depo-Provera) injection with the failure rate of 0.3%; copper IUD with the failure rate of 0.6%; condom with spermicide with the failure rate of 4-6%; condom without spermicide of 14%; and female condom of 21%. Due to its low failure rate, women with epilepsy are advised to use mechanical contraception that is intrauterine device (IUD). This contraception within the uterus acts locally with the use for five years.[21] In this case report, patient used intrauterine device (IUD) which was installed in Obstetric Clinic at January 5 2016.

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5. Disclosure

None

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