Samsun Sağ Bil Der, 2019;4(2):38-43

PREGNANCY AND EPILEPSY

Murat ALAN[1*], Muhammet Ali ORUÇ[2]

ABSTRACT

Epilepsy is one common neurological diseases. Epilepsy patients should be closely followed in terms of maternal and infant health if they become pregnant. Family physician, neurologist and gynecologist should be done in cooperation. Good management of the disease during diagnosis, treatment and follow-up is important for public health. These patients should be evaluated more carefully in primary health care facilities and should be referred to the relevant specialist if necessary.

Keywords: *Epilepsy; pregnancy; antiepileptic drug; status epilepticus.*

Gebelik ve Epilepsi

ÖZET

Epilepsi yaygın bir nörolojik hastalıktır. Epilepsi hastaları hamile kalırlarsa anne ve bebek sağlığı açısından yakından takip edilmelidir. Aile hekimi, nörolog ve jinekolog işbirliği içinde yapılmalıdır. Tanı, tedavi ve takip sırasında hastalığın iyi yönetimi halk sağlığı için önemlidir. Bu hastalar birinci basamak sağlık kuruluşlarında daha dikkatli değerlendirilmeli ve gerekirse ilgili uzmana yönlendirilmelidir.

Anahtar Kelimeler: *Epilepsi; gebelik; antiepileptik ilaç; status epileptikus.*

[1]Health Sciences University, Tepecik Education and Research Hospital, Department of Gynecology and Obstetrics, İzmir, Turkey
[2]Ahi Evran University, Faculty of Medicine, Department of Family Medicine, Kirsehir, Turkey
Sorumlu yazar: Murat Alan*

INTRODUCTION

Epilepsy is a common neurological disease. Women with epilepsy constitute 0.5-1% of all pregnancies (Harden, Meador & Pennell, 2009; Edey, Moran & Nashef, 2014). The risk of having seizures during pregnancy is 1.2% in the US (Zack & Kobau, 2017). There is no general rule for epileptic pregnant patient' follow-up.A patient with known epilepsy may become pregnant, while it is not rare that the first seizure occurs during pregnancy. Seizures can be caused by many factors. Infectious, vascular, malignant, metabolic, toxic and many other conditions can cause seizures. Another reason for increase in seizures in pregnancy is changes in blood biochemistry. Identifying the underlying cause is very important in diagnosis, treatment and prognosis. Mothers with epilepsy should be more closely followed during pregnancy and infant follow-ups in primary care centers. This is very important in terms of maternal and infant mortality and morbidity.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Epilepsy is defined as two or more unprovoked seizures. According to World Health Organization, epilepsy is the most common primary disease of the brain (Chang & Williams, 2016). The disease has two age-specific peaks, one among very young persons and a second among very elderly. According to the International League Against Epilepsy (ILAE) classification, seizures are divided into two major groups, focal and generalized. Focal seizures are grouped into temporal, frontal, occipital and parietal seizures. Generalized seizures are classified into absence, myoclonic, clonic, tonic, tonic-clonic and atonic seizures (Fisher , Cross & D'Souza,2017).(Table 1).

Table 1 Classification of seizures

Classification of seizures
Focal seizures
Temporal lobe seizures
Frontal lobe seizures
Temporal lobe seizures
Parietal lobe seizures
Generalized seizures
Absence
Typical absence
Atypical absence
Myoclonic
Clonic
Tonic
Tonic-clonic
Atonic

Patients' histories, physical and neurological examination findings and diagnostic studies are very important in diagnosis. A good description of the seizure may be the most important factor at the time of diagnosis in many patients. In general, a video recording of the seizure activity may clearly reveal the clinical picture. It should first be decided whether the clinical condition is a seizure in a patient with clinical findings such as jerks, fainting and loss of consciousness. In some patients, there may be overlapping clinical findings. Epileptic seizures may coexist with pseudoseizures.

Syncope is defined as loss of consciousness due to a transient decrease in cerebral blood flow. A good anamnesis and examination can distinguish between a seizure and syncope in many patients. Syncope is one of the most common conditions confused with seizures in differential diagnosis. Syncope is defined as loss of consciousness due to a transient decrease in cerebral blood flow. A good anamnesis and examination can distinguish between a seizure and syncope in many patients. In spite of distinct underlying pathophysiological processes, syncope and seizure share some clinical characteristics which may lead to diagnostic confusion. Both may occur suddenly without warning, both may result in injury and convulsive jerks may occur in both. Though sometimes it is difficult to differentiate epilepsy from syncope, the symptoms surrounding the loss of consciousness may be useful in clinical practice(Edey, Moran & Nashef, 2014). The symptoms appear immediately after turning their head to one side, and the symptoms described before falling off increase the suspicion of syncope. In order to differentiate syncope from epilepsy, EEG and ECG are the first tests to be performed.

Changes in seizures are known occur due to the effect of reproductive cycle in many epileptic women. Seizures are clustered around a specific phase in half of the patients. These changes are largely due to the effect of ovarian steroids on the central nervous system (Bora, 2008). The condition is referred to as catamenial epilepsy when seizure frequency is related to menstrual cycle. There is an increase in seizures during the period from 4 days prior to 6 days after the menstruation (Herzog , Klein & Ransil,1997; Lim, Foldvary & Mascha , 2001).

At-risk pregnancy follow-up should be performed when an epileptic patient becomes pregnant. The gestation period is expected to be 2-3 times more problematic compared to general population (Bora, 2008). It is critical that neurologists, family practitioners and gynecologist work together. The chance of delivering a healthy child is 98% in general population, while it is 92-96% in epileptic patients (Tettenborn, Genton & Polson , 2002). Teratogenicity may be caused by treatments received by the mother, seizures during pregnancy and the pathologies causing epilepsy.

FOLLOW-UP OF EPILEPTIC PATIENTS:

There is no general rule for patient follow-up. Clinical findings may vary from patient to patient. Disease activity may increase in some patients while it may decrease in others during pregnancy. The same applies for delivery and lactation periods.

Prepregnancy period

Oral contraceptives are currently one of the most commonly used methods of contraception. Contraception is an important concern for women with epilepsy. Pharmacokinetic interactions between antiepileptic drugs and oral contraceptives are bi-directional. Steroid hormones and enzyme-inducing antiepileptic drugs are substrates for the cytochrome P450 enzyme system. There are evidences indicating that phenytoin, carbamazepine, primidone, phenobarbital, topiramate and particularly oxcarbazepine reduce the efficacy of oral contraceptives. Consequently, the concomitant use of hormonal contraceptives and antiepileptic drugs may pose a risk for unexpected

pregnancies and seizures. This should not be ignored in patient care and should be carefully evaluated by family practitioners. (Reimers, Brodtkorb & Sabers, 2015).

There are evidences that congenital malformations are less common in women who use folic acid in prepregnancy period and during the first trimester. Folic acid is recommended even though its levels are normal. It is recommended that the intake of folic acid (1-4 mg/day) should start 3 months before a planned pregnancy and should continue during of pregnancy. It is known that this supportive treatment given to healthy mothers is even more valuable in women with epilepsy (Shannon, Alberg & Nacul, 2014; Winterbottom, Smyth & Jacoby,2009).

Treatments currently received by epileptic women should be reviewed in case of a planned pregnancy. Seizure type and frequency should be clearly defined. Pregnancy may be delayed for a while if seizures are not under control. A minimum of 9-12-month seizure-free period is important for a seizure-free pregnancy(Zahn,Morrel & Collins, 1998; Patsalos,Berr & Bourgeois,2008; Vajda, Hitchcock & Graham, 2008). Appropriate treatment should be planned based on the clinical findings and the electroencephalography (EEG) result of the patient. The risks should be discussed with the patient. Lowering the dose or switching to drugs with a lower teratogenic risk may be considered when deemed necessary. In multiple prospective studies, it was found that valproic acid (VA) and phenobarbital confer higher risks for congenital malformations. The risk is even higher with combination treatments. Studies do not provide any high-level evidence to support the use of any anti-seizure drugs (Chang & Williams, 2016).

Pregnancy period

If a patient with epilepsy presents after conception and if her seizures are under control with monotherapy, the treatment should not be changed. In a patient receiving polytherapy, switching to monotherapy can be tried depending on the clinical findings. Polytherapy should be continued in at-risk patients (Morrell,1998).

Blood levels of antiepileptic drugs (AEDs) play an important role in patient follow-up. Blood AED levels may decrease, particularly due to an increase in plasma volume. The blood concentration value should not be the sole determinant in a patient whose seizures are under control. The main determinant is the clinical picture of the patient. AED levels may be more useful in patients without seizure control and with poor compliance.

No changes occur in seizure frequency and characteristics in majority of patients during pregnancy. The main factor causing changes is a decrease in patient compliance. Increase in seizures is not associated with disease duration or seizure characteristics. However, it may be related to blood drug levels at the onset of pregnancy (Morrell & Montouris, 2004; Crawford, 2011). Safe plasma concentration ranges of AEDs are generally narrow. Therefore, patients should pay the most attention to compliance.

Another reason for increase in seizures is changes in blood biochemistry. Increased plasma volume and decreased protein levels may decrease the plasma concentrations of total and free AEDs. Sleep disturbance and anxiety may also increase seizure frequency (Morrell & Montouris, 2004; Crawford, 2001; Crawford,1997; Kaneko, 2000; Reisinger, Newman & Loring, 2013). A generalized seizure during pregnancy may harm both the mother and the fetus more than an AED. It may cause prolonged seizures and status epilepticus (SE) in mothers. Generalized seizures may lead to temporary decreases in placental blood flow, leading to an increased risk of abortion and low birth weight (Chang & Williams, 2016; Borgelt, Hart & Bainbridge, 2016).

Labor and postpartum period

Normal vaginal delivery is possible in a patient whose seizures are under control and who is on a regular treatment, if there are no gynecological problems that would preclude a normal delivery. In these patients, the risk of seizure is 1-2% during delivery and within 24 hours after birth. It is important that AEDs are taken regularly during the labor period (Crawford, 2001; Crawford, Appleton & Betts,1999). The rate of caesarean section is high in women taking AEDs. Preeclampsia, gestational diabetes, preterm labor and excessive bleeding after delivery may also be seen. Low Apgar scores, perinatal death and stillbirth are more common in the offspring of women with epilepsy taking AEDs. These patients require more interventions (forceps and vacuum) during normal delivery (MacDonald , Bateman & McElrath, 2015; Meador, Pennell & Harden, 2008; Tomson, Battino & Bonizzoni, 2006; Viale, Allotey & Cheong-See, 2015; Bromley, Weston & Adab, 2014). Therefore, possible risks to both the mother and the child should be considered and necessary precautions should be taken during delivery.

Cesarean section should be preferred if the mother has any neurological or mental problems and her seizures are not under control soon before delivery. A generalized seizure during delivery is an indication for emergency cesarean section.

Lactation and post-lactation periods

The transplacental passage rate of AEDs is much lower compared to excretion into milk. Therefore, breastfeeding should be encouraged (Munshi & Munshi, 2012). Studies investigating the effects of breast milk in epileptic women found higher IQ scores in breast-fed children (Meador, 2014; Meador, Baker & Browning, 2010). It is believed that the dose of AED excreted into milk has no unfavorable effects on nervous system development (Meador, Baker & Browning, 2010; Veiby, Engelsen & Gilhus, 2013; Johannessen, Helde & Brodtkorb, 2005; Ohman, Vitols & Luef, 2002; Ohman, Vitols, Tomson, 2005). During early infancy, low rate of elimination due to incomplete hepatic development may rarely lead to drug accumulation, causing negative effects. Attention should be paid to this condition in infants with impaired hepatic function. Phenobarbital and primidone should be paid the most attention in this respect (Bora, 2008). Lamotrigine may also cause risk when used in combination with VA (Crawford, 2001;Tomson, 2005).

ANTIEPILEPTIC TREATMENT:

During pregnancy

If seizure control is achieved in patients with epilepsy, AED treatment should be continued during and after pregnancy. In patients without any seizures for the

previous 2 to 4 years, stopping the treatment before pregnancy may be considered based on clinical and laboratory findings. Seizure frequency may increase in 20-30% of patients during pregnancy. Among patients with no seizures during the 9-month period before pregnancy, 84-92% may be completely seizure-free during pregnancy (Harden, Hopp & Ting, 2009).

The prepregnancy treatment and clinical findings of the patient should be well evaluated in case of a planned pregnancy. Switching to monotherapy may be considered if the clinical features are appropriate. Patients receiving treatments with high teratogenicity such as VA may be switched to less teratogenic treatments based on the clinical findings. Physicians should not hurry to make these changes and seizure type, seizure-free period, accompanying diseases, EEG findings and blood drug levels should be evaluated together.

In status epilepticus

In addition to the risks to the mother, SE may cause fetal hypoxia by decreasing placental blood flow (Goodwin, 1947; Kaplan, Norwitz, Ben-Menachem, 2007). During pregnancy, there is no increased risk of SE compared to other periods (Harden, Hopp & Ting, 2009). The causes of SE may include eclampsia, posterior reversible encephalopathy syndrome, cortical venous thrombosis and autoimmune encephalitis (Rajiv & Radhakrishnan, 2017). The most common reason is noncompliance to medical treatment.

In SE, lorazepam treatment is more preferred than midazolam and can be a good choice for initial treatment (Karnad & Guntupalli, 2005). Exposure to VA, phenobarbital and phenytoin during the first trimester may have adverse effects on the fetus. Levetiracetam may be more appropriate in these cases (Molgaard-Nielsen, 2011). Magnesium and phenytoin can be used for seizures and eclampsia. However, other agents may also be required (Duley, Henderson-Smart & Chou, 2010). When seizures cannot be controlled, general anesthesia can be life-saving for the mother.

Drug side effects

The risk of congenital malformations is much lower in patients using monotherapy compared to patients receiving polytherapy (Gerard & Samuels, 2017; Buhimschi & Weiner, 2009). Teratogenic effect is highest with VA and phenytoin. This effect is much lower with drugs such as levetiracetam and lamotrigine(Cheschier, 2003; Practice Parameter,1998).

Table 2. Teratogenicity of antiepileptic drugs (Gerard & Samuels, 2017; Bollig & Jackson , 2018; Hart & Sibai, 2013; Aminoff & Douglas, 2014).

Table 2 Teratogenicity of antiepileptic drugs

Drug	Teratogenicity rate (%)	Major congenital anomaly
Phenytoin	0.7-7.0	Fetal hydantoin syndrome, intrauterine growth retardation, cardiac malformation, neural tube defect, hypospadias
Carbamazepine	2-6	Orofacial defect and cardiac malformations
Valproic acid	4-14	Neural tube defect, orofacial defect, fetal valproate syndrome, polydactyly, hypospadias
Lamotrigine	2-5	Cleft palate, cleft lip
Levetiracetam	0-2	Non-specific
Topiramate	3-4	Cleft palate, cleft lip
Gabapentin	0-6	Non-specific
Phenobarbital	1-6	Cardiac malformations, cleft lip, cleft palate, cognitive effects

Increase in congenital malformations is not expected in patents receiving polytherapy if VA and topiramate are not used (Vajda, O'Brien & Graham, 2018). VA used alone or in combination with other drugs may lead to adverse neurodevelopmental outcomes in the fetus. Oxcarbazepine and lamotrigine are associated with an increased rate of autism (Veroniki, Rios & Cogo, 2017).

PREGNANCY COMPLICATIONS ASSOCIATED WITH EPILEPSY

Pregnancy in women with epilepsy should be considered as an at-risk pregnancy. Most of the pregnant epileptic women have a normal pregnancy without any change in seizure frequency. More than 90% of these women give birth to healthy children. Possible complications include fetal abortion, congenital malformations, preterm birth, psychomotor development retardation and low birth weight. Maternal complications may include increased postpartum bleeding, high cesarean section rate and interventional labor (Borgelt, Hart & Bainbridge, 2016; Bollig & Jackson, 2018).

The classical AEDs (carbamazepine, phenobarbital, phenytoin, primidone, VA) are in Category D based on their effects on the fetus. However, these drugs may be used by conducting a benefit-harm assessment.

INFANTS BORN TO EPILEPTIC WOMEN

It was reported that antiepileptic drugs used during pregnancy can have effects on fetal major malformations as well as on neurodevelopmental processes and the rate of mental retardation, negative cognitive effects and the need for special education are higher in the exposed children (Vajda, O'Brien & Graham, 2018). Children of mothers taking VA were found to have lower IQ scores and lower memory skills compared to other drugs. This effect of VA

increases with the dose. Phenobarbital use in the last trimester negatively affects cognitive abilities such as attention and memory. Phenytoin, especially when used in a polytherapy and with a high dose, has a more prominent mental effect (Vajda, O'Brien & Graham, 2018; Veroniki, Rios & Cogo, 2017).

CONCLUSION

Maternal and infant health is one of the most fundamental elements of public health. Epilepsy is a common disease in women of childbearing age. Epileptic women should be more closely followed by family practitioners, neurologists and gynecologist during pregnancy compared to pregnant women without epilepsy. The cases can be well managed before, during and after pregnancy with an approach focused on both the mother and the infant.

ACKNOWLEDGMENTS

The authors thank Murat Terzi, MD, for data management at the Department of Neurology, Ondokuz Mayis University. No conflict of interest was declared by the authors. The authors declared that this study received no financial support.

REFERENCES:

Aminoff, M.J., Douglas, V.C.(2014). *Neurologic disorders*. In: Creasy RK, Resnik R, Iams JD, editors. Creasy & Resnik's maternal-fetal medicine: principles and practice. 7th edition. Philadelphia: Elsevier; 2014. p. 1100–3.

Bollig, K.J, Jackson, D.L. (2018).Seizures in Pregnancy. *Obstet Gynecol Clin North Am*., 45(2),349-367.

Bora, İ.(2008). *Epilepsi*. S: 369-383.

Borgelt, L.M., Hart, F.M., Bainbridge, J.L.(2016). Epilepsy during pregnancy: focus on management strategies. *Int J Womens Health*, 19(8),505-517.

Bromley, R., Weston, J., Adab, N, et al.(2014). Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. *Cochrane Database Syst Rev*, (10):CD010236.

Buhimschi, C., Weiner, C.(2009). Medication in pregnancy and lactation: part 1. Teratology. *Obstet Gynecol*, 113:166.

Chang, A., Williams, B.(2016). *Current Diagnosis and Treatment*. Second Edition, S47-62.

Cheschier, N. (2003). ACOG practice bulletin. Neural tube defects. *Int J Gynaecol Obstet*, 83(1),123–33.

Crawford, P.(1997). Epilepsy and pregnancy:goog manegement reduces the risk. *Professional care of mather and child*, 7(1).

Crawford, P., Appleton, R., Betts, T., Duncan, J., Guthrie, E., Morrow, J.(1999). *Best practice guidelines for the management of women with epilepsy*. The Women with Epilepsy Guidelines Development Group. Seizure,8(4),201-17.

Crawford, P.(2001). CPD-Education and self-assessment: Epilepsy and pregnancy. *Seizure*, 10(3),212-9.

Duley, L., Henderson-Smart, D.J., Chou, D.(2010). Magnesium sulphate versus phenytoin for eclampsia. *Cochrane Database Syst Rev*, (10),CD000128.

Edey, S., Moran, N., Nashef, L.(2014). SUDEP and epilepsy-related mortality in pregnancy. *Epilepsia*, 55(7),e72–4.

Fisher, R.S., Cross, J.H., D'Souza, C., French, J.A, Haut, S.R. & Higurashi, N.(2017). Instruction manual for the ILAE 2017 operational classification of seizure types. *Epilepsia*, 58(4), 531-542.

Gerard, E.E., Samuels, P.(2017). *Neurologic disorders in pregnancy*. In: Gabbe SG, editor. Obstetrics: normal and problem pregnancies. 7th edition. Philadelphia: Elsevier, p. 1030–56.

Goodwin, J.F. (1947). Status epilepticus complicating pregnancy. *Br Med J*,2,332–3.

Harden, C., Meador, K., Pennell, P, et al.(2009). Practice parameter update: management issues for women with epilepsy—focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology*,73(2),133–41.

Harden, C., Hopp, J., Ting, T., et al.(2009). Practice parameter update: management issues for women with epilepsy–focus on pregnancy (an evidence-based review): obstetrical complications and change in seizure frequency: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology*, 73(2),126–32.

Hart, L., Sibai, B. (2013). Seizures in pregnancy: epilepsy, eclampsia, and stroke. *Semin Perinatol*, 37,207–24.

Herzog, A.G., Klein, P., Ransil, B.J.(1997). Three patterns of catamenial epilepsy. *Epilepsia*, 38(10): 1082-8.

Johannessen, S., Helde, G, Brodtkorb, E.(2005). Levetiracetam concentrations in serum and in breast milk at birth and during lactation. *Epilepsia*, 46(5),775–7.

Kaneko, S.(2000). Epilepsy, pregnancy, and the child. *Epilepsia*, 41 Suppl 9:8-13.

Kaplan, P.W., Norwitz, E.R., Ben-Menachem, E.(2007). Obstetric risks for women with epilepsy during pregnancy. *Epilepsy Behav*, 11:283–91.

Karnad, D.R., Guntupalli, K.K.(2005). Neurologic disorders in pregnancy. *Crit Care Med*,33(10),S362–71.

Lim, L.L., Foldvary, N., Mascha, E., Lee, J.(2001). Acetazolamide in women with catamenial epilepsy. *Epilepsi*,. 42(6):746-9.

MacDonald, S., Bateman, B., McElrath, T, et al.(2015). Mortality and morbidity during delivery hospitalization among pregnant women with epilepsy in the United States. *JAMA Neurol*, 72,981–8.

Meador, K., Baker, G., Browning, N, et al.(2010). Effects of breastfeeding in children of women taking antiepileptic drugs. *Neurology*, 75(22), 1954–60.

Meador, K., Pennell, P., Harden, C., et al. (2008). Pregnancy registries in epilepsy: a consensus statement on health outcomes. *Neurology*, 71(14),1109.

Meador, K.(2014). Breastfeeding and antiepileptic drugs. *JAMA*,311(17),1797–8.

Molgaard-Nielsen, D.(2011). Newer-generation antiepileptic drugs and the risk of major birth defects. *J Am Med Assoc*, 305(19): 1996–2002.

Morrell, M.J. (1998). Guidelines for the care of women with epilepsy. *Neurology,* 51(5 Suppl 4), S21-7.

Morrell, M.J., Montouris, G.D. (2004). Reproductive disturbances in patients with epilepsy. *Cleve Clin J Med.*, 71 Suppl 2,S19-24.

Munshi, A., Munshi, S.(2012). Neurological diseases. In: Malhotra N, Puri R, Malhotra J, editors. *Donald school manual of practical problems in obstetrics.* 1st edition. New Delhi (India): Jaypee Brothers Medical Publishers (P) Ltd, p 281–3.

Ohman, I., Vitols, S., Tomson, T. (2005). Pharmacokinetics of gabapentin during delivery, in the neonatal period, and lactation: does a fetal accumulation occur during pregnancy? *Epilepsia*,;46(10),1621–4.

Ohman, I., Vitols, S., Luef, G., et al.(2002). Topiramate kinetics during delivery, lactation, and in the neonate: preliminary observations. *Epilepsia*, 43(10),1157–60.

Patsalos, P. N., Berr, D.J., Bourgeois, B. F. D., et al.(2008). Antiepileptic drugs — best practice guidelines for therapeutic drug monitoring: ILAE Commission on Therapeutic Strategies.Epilepsia, 49 (7): 1239E1276.

Practice Parameter.(1998). management issues for women with epilepsy. Report of the quality standards subcommittee of the American Academy of Neurology. *Neurology*,51(4),944.

Rajiv, K.R., Radhakrishnan, A.(2017). Status epilepticus in pregnancy: Etiology, management, and clinical outcomes. *Epilepsy Behav*.,76,114-119.

Reimers, A., Brodtkorb, E., Sabers, A.(2015). Interactions between hormonal contraception and antiepileptic drugs: Clinical and mechanistic considerations. *Seizure,* 28,66-70.

Reisinger, T.L., Newman, M., Loring, D.W., Pennell, P.B., Meador, K.J.(2013). Antiepileptic drug clearance and seizure frequency during pregnancy in women with epilepsy. *Epilepsy Behav.*,29(1),13–18.

Shannon, G.D., Alberg, C., Nacul, L., Pashayan, N.(2014). Preconceptiion healthcare and congenital disorders: systematic review of the effectiveness of preconception care programs in the prevention of congenital disorders. *Matern Child Health J*., 18(6),1354-79.

Tettenborn, B., Genton, P., Polson, D. (2002). Epilepsy and women's issues: an update. *Epileptic Disord*. 4 Suppl 2:S23-31.

Tomson, T., Battino, D., Bonizzoni, E, et al.(2011). Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. *Lancet Neurol* ,10(7), 609.

Tomson, T. (2005). Gender aspects of pharmacokinetics of new and old AEDs: pregnancy and breast-feeding. *Ther Drug Monit*., 27(6), 718-21.

Vajda, F.J., Hitchcock, A., Graham, J., O'Brien, T., Lander, C., Eadie, M.(2008). Seizure control in antiepileptic drug-treated pregnancy. *Epilepsia*, 49(1),172–176.

Vajda, F.J.E., O'Brien, T.J., Graham, J.E., Hitchcock, A.A., Lander, C.M., Eadie, M.J. (2018). Antiepileptic drug polytherapy in pregnant women with epilepsy. *Send to Acta Neurol Scand.*, 24. doi: 10.1111/ane.12965.

Veroniki, A.A., Rios, P., Cogo, E., Straus, S.E., Finkelstein, Y., & Kealey, R. (2017). Comparative safety of antiepileptic drugs for neurological development in children exposed during pregnancy and breast feeding: a systematic review and network meta-analysis. *BMJ Open.*, 20,7(7):e017248.

Viale, L., Allotey, J., Cheong-See, F., et al. (2015). Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis. *Lancet*, 386(10006):1845.

Veiby, G., Engelsen, B., Gilhus, N.(2013). Early child development and exposure to antiepileptic drugs prenatally and through breastfeeding: a prospective cohort study on children of women with epilepsy. *JAMA Neurol*,70(11),1367–74.

Winterbottom, J., Smyth, R., Jacoby, S., & Baker, G. (2009). The effectiveness of preconception counseling to reduce adverse pregnancy outcome in women with epilepsy: What's the evidence? *Epilepsy & Behavior*, 14, 273–279.

Zack, M., Kobau, R.(2017). National and state estimates of the numbers of adults and children with active epilepsy United States, 2015. *MMWR Morb Mortal Wkly Rep*, 66, 821–5.

Zahn, C.A., Morrell, M.J., Collins, S., et al.(1998) Management of issues for women epilepsy.A review of the literature. Neurology, 51: 949-956