Pregnancy outcome in women with epilepsy: A pilot study in Oman

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Abstract
Background: Treatment of pregnant women with epilepsy is a challenge as the benefit of the treatment has to be weighed against the adverse fetal and maternal effects of the drug.
Objective: To determine the malformation risk of fetus exposed to antiseizure medication during pregnancy and to assess other fetal outcomes including pregnancy losses, growth retardation in fetus.
Methods: This is a retrospective observational study from patient records. Both mother and infant data from records were retrospectively collected and interpreted. Any disparity and missing information was collected by directly contacting the concerned patients.
Results: A total of 137 pregnancies in women with epilepsy were studied. The incidence of major congenital malformation was 6.8%. There were 13 pregnancy losses (9.4%) and 12 preterm deliveries (87.6%)
Conclusion: The observations of adverse fetal outcomes were comparable to the larger studies conducted. More importance to women with epilepsy and their treatment should be given. There is a need for larger and comparative regional studies in pregnant females with epilepsy.

Keywords: women with epilepsy, congenital malformations, seizure in pregnancy

Introduction

Women with epilepsy have a lot of concerns during pregnancy including the seizure behaviour during pregnancy, risk of pregnancy losses and adverse effects of seizure and anti-seizure medication on the mother and the fetus. Evidence suggests a definite increased risk of major congenital malformation in women taking anti-seizure medication. Newer anti-seizure drugs are being introduced and their role in pregnancy is being questioned. Randomised controlled trials are not feasible in pregnancy with epilepsies. Due to these reasons there is a need for continuous observational studies in women with epilepsy. Many countries have established pregnancy registries for women with epilepsy. There is a need for larger studies to be done in Middle East to assess for regional differences in observations.

Methods

A retrospective study was conducted in women with epilepsy who were followed in our hospital during the ten year period from 2010 to 2019. The patient data was collected from electronic medical records in the hospital and the data for the new born babies were collected from the medical records of the new borns. Missing data was collected through direct or telephonic interview. Data for any co morbid illness was also collected. We received the ethical approval from the regional committee (ref-RERAC MH/DHGS/NBG/2023199933/2020).
Information on demographics, comorbidities, exposure to other teratogens and medications were also collected.
Primary outcome was incidence of congenital malformation in babies born to women with epilepsy. Secondary outcome were maternal seizure control, pregnancy losses and preterm delivery in pregnant women with epilepsy.

Preterm delivery is birth occurring before 37 weeks of gestation. Low birth weight is birth weight below 2.5 kg regardless of gestational age. Congenital anomalies are defined as any structural or chromosomal anomalies or inborn errors of metabolism noted by the attending paediatrician at birth or subsequently during follow up visits. A major malformation was defined as a structural abnormality with surgical, medical, or cosmetic importance [1].

Results

Since more than one pregnancy is frequent in this study, we take each individual pregnancy as separate. In 27 pregnancies (19.7%) patients were on more than one drug while 90 patients (80.3%) were on monotherapy. In the polytherapy group 25 were on two drugs and two were on three drugs. The most frequently used antiepileptic was carbamazepine (65, 47%), followed by Levetiracetam (25, 18.2%) and then sodium valproate (24,17.5%). No antiepileptics were taken during 20 pregnancies mainly because the patients were concerned about the fetal effect of antiepileptics. 13(65%) out of the untreated group had seizure during pregnancy period. 25 of the 117 (21%) treated cases had seizure during pregnancy. 13 pregnancies ended in abortion (9.4%). Of these seven were having seizure. 12 babies were delivered preterm. OF these ten were on antiseizure medications while two were not receiving any medications.

The total congenital anomalies reported in females with epilepsy were 17 (12.4%). These included minor and major congenital anomalies, deformations and chromosomal anomalies. When considering only the major congenital malformations the number was ten. Of these, two patients were not on any treatment despite having seizures. Excluding the two who were not on drugs, the major congenital malformation was seen in eight out of the 117 pregnancies (6.8%) who were exposed to antiseizure drugs.

65 patients were on carbamazepine either as mono or polytherapy. Five cases of fetal anomaly were reported (7.6%). These were one case of laryngomalacia, one polydactyly, one trisomy 18 and one hypospadias. One patient with cardiac anomaly was on polytherapy (levetiracetam with carbamazepine).

24 patients were on valproate therapy. No major congenital malformation was reported in the valproate treated group. One neonate had vaginal tag, another had tongue tie and one patient on polytherapy had congenital dislocation of hip (12.5%).

Two cases of cardiac anomaly were reported with levetiracetam. One patient was on polytherapy with carbamazepine (earlier mentioned).

Lamotrigine which is currently considered as a safer drug in pregnancy was used in 22 pregnancies. One case of cardiac anomaly and one congenital dislocation of hip was reported in patients on Lamotrigine monotherapy.Phenytoin was used in three cases and one fetus had cardiac anomaly. Phenobarbitone was used only in one pregnancy and no fetal effect was noted.

There were 12 low birth weight babies in the study group. Among these, three mothers were not taking antiseizure drugs, five were on monotherapy and four on polytherapy. Among the monotherapy group two were on carbamazepine, two were on levetiracetam and one was on sodium valproate.

Discussion

Treating women with epilepsy is a challenge in its own and choice of treatment not only depends on the seizure type and severity but also on the future and present reproductive plans of the patient. The decisions are more complex during pregnancies. Recurrent seizures during pregnancy can lead on to fetal loss and fetal hypoxia. On the other hand drugs for seizure can increase the risk of congenital malformation for the fetus. Optimal management of seizure in mother without causing teratogenic risk to fetus is the aim. Over the past years the management of epilepsy in women belonging to child bearing ages has changed. Studies have revealed that the risk of congenital malformation in women taking antiseizure drugs during pregnancies is higher (4-7 %) than that for the normal population (1- 2%) [2, 15]. A study from UAE reported an incidence of 9.3% congenital malformations in women exposed to antiseizure drugs. In our study 6.8 % pregnancies exposed to antiseizure drugs had major congenital malformations which is within the range observed in larger studies.

Most data for pregnancy outcome in women with epilepsy is obtained from large prospective registry studies. EURAP registry which collects data from over 42 countries has reported a dose dependent increase in risk of congenital malformations with antiseizure drugs Lamotrigine, valproate, carbamazepine and phenobarbitone [2]. North American Antiepileptic Drug Pregnancy Registry reported dose dependent risk of congenital malformation only for valproate [3]. UK and Ireland epilepsy and pregnancy registry reported a dose dependency in congenital malformation with valproate and carbamazepine [4]. The use of newer antiseizure drugs like levetiracetam and lamotrigine has increased recently. It is pertinent to look into the fetal risk associated with these drugs. These drugs are mostly recommended for women with epilepsy and in pregnancy, due to the fewer adverse effects reported.

Teratogenicity of valproate is well established. Studies have shown a dose dependent increase in risk of malformation with valproate [6]. It is associated with increased risk of neural tube defects, cardiac malformations, cleft palate and hypospadias [3, 7]. Moreover prenatal exposure to valproate has been linked to developmental intellectual disabilities including autism [5]. The American epilepsy society has recommended in its practice parameter to avoid valproate in first trimester if possible. Still it is being used because of its usefulness in many idiopathic generalised epilepsies. Only minor malformation was reported with valproate in our study. This may be due to the lower dose of valproate used in the patients. Also the sample size is low.

Exposure to carbamazepine is associated with increased risk of neural tube defects, cleft palate, hypospadias and cardiac malformations [8, 10]. Though lower than valproate significant dose dependent teratogenic effect for carbamazepine was seen in some studies [2]. Many studies have reported an increased risk of cleft palate in fetus exposed to topiramate during pregnancy [3, 8, 9]. Risk of malformation is more in cases exposed to topiramate as part of polytherapy [9]. None of our patients were on topiramate during pregnancy.

Lamotrigine is considered as relatively safe during pregnancy. The incidence of congenital malformation with lamotrigine in EURAP study was 2.9% [2]. In our study we had one cardiac anomaly reported in an infant exposed prenatally to Lamotrigine. Levetiracetam also has lesser incidence of fetal side effects. The incidence of malformation in EURAP study was 2.8% while in North American registry

was 2.4%. The UK and Ireland registry reported the lowest risk (0.7%). One cardiac anomaly was reported in our patient who was on polytherapy with Levetiracetam and Carbamazepine while another patient on Levetiracetam monotherapy had inguinal hernia in the new born.

Seizure recurrence during pregnancy is a major concern for women with epilepsy. Prepregnancy seizure is a reliable predictor of seizure during pregnancy and peripartum period and use of Valproate is associated with lowest risk of seizure recurrence [13]. Data from Australia did not find any significant association between active seizures at outset of pregnancy and congenital malformations in fetus.[14] In our study 65% of the non-treated and 21 % of the treated group had seizure during pregnancy.

Our study had its own limitations. It was retrospective and a purely observational study. No control group was available. Hence risk assessment cannot be made. Also the sample size was low. Further studies regarding the risk and benefit assessment of antiseizure drugs is needed. We had cases of congenital malformations in the lamotrigine and levetiracetam treated patients. These are considered relatively safe as per current studies. There is a need for larger studies in this population to assess the safety of these drugs.

A crucial part in treating women with epilepsy is to identify the minimum therapeutic dose to control seizures, preferring monotherapy rather than polytherapy. If polytherapy is needed, it is important to use the combinations which have the least effect on fetus. Preconception planning, counselling and disease management is essential to reduce the fetal and maternal risk.

Conclusion

There are only a few studies regarding pregnancy outcome in women with epilepsy in Arab region. This may be the first study done in Omani females with epilepsy and calls for prospective study and establishment of registries for pregnant women with epilepsy in Arab population.

References

1. Holmes LB. Need for inclusion and exclusion criteria for the structural abnormalities recorded in children born from exposed pregnancies. Teratology. 1999; 59(1):1-2. doi: 10.1002/(SICI)1096-9926(199901)59:1<1::AID-TERA1>3.0.CO;2-L. PMID: 9988874.
2. Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Perucca E, *et al*. EURAP Study Group. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. Lancet Neurol. 2018; 17(6):530-538. doi: 10.1016/S1474-4422(18)30107-8. Epub 2018 Apr 18. PMID: 29680205.
3. Hernández-Díaz S, Smith CR, Shen A, Mittendorf R, Hauser WA, Yerby M, *et al*. North American AED Pregnancy Registry; North American AED Pregnancy Registry. Comparative safety of antiepileptic drugs during pregnancy. Neurology. 2012; 78(21):1692-9. Doi: 10.1212/WNL.0b013e3182574f39. Epub 2012 May 2. PMID: 22551726.
4. Campbell E, Kennedy F, Russell A, Smithson WH, Parsons L, Morrison PJ, *et al*. Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers. J Neurol Neurosurg Psychiatry. 2014; 85(9):1029-34. Doi: 10.1136/jnnp-2013-306318. Epub 2014. PMID: 24444855.
5. Meador KJ, Baker GA, Browning N, *et al*. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013; 12(3):244-252. doi:10.1016/S1474-4422(12)70323-X
6. Vossler DG. Comparative Risk of Major Congenital Malformations with 8 Different Antiepileptic Drugs: A Prospective Cohort Study of the EURAP Registry. Epilepsy Curr. 2019; 19(2):83-85. Doi: 10.1177/1535759719835353
7. Jentink J, Loane MA, Dolk H, Barisic I, Garne E, Morris JK, *et al*. EUROCAT Antiepileptic Study Working Group. Valproic acid monotherapy in pregnancy and major congenital malformations. N Engl J Med. 2010; 362(23):2185-93. Doi: 10.1056/NEJMoa0907328. PMID: 20558369.
8. Pierre Blotière, Fanny Raguideau, Alain Weill, Elisabeth Elefant, Isabelle Perthus, Véronique Goulet, *et al*. Risks of 23 specific malformations associated with prenatal exposure to 10 antiepileptic drugs. Neurology. 2019; 93(2):e167e180 DOI: 10.1212/WNL.0000000000007696
9. Hunt S, Russell A, Smithson WH, Parsons L, Robertson I, Waddell R, *et al*. UK Epilepsy and Pregnancy Register. Topiramate in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register. Neurology. 2008; 71(4):272-6. Doi: 10.1212/01.wnl.0000318293.28278.33. PMID: 18645165.
10. Jentink J, Dolk H, Loane MA, Morris JK, Wellesley D, Garne E, *et al*. Intrauterine exposure to carbamazepine and specific congenital malformations: systematic review and case-control study. BMJ. 2010; 341:c6581.
11. Alsaadi T, Kassie S, Farook F, Nasreddine W, Wani S, Saleh B. Antiseizure drugs use during pregnancy and congenital malformations: A retrospective review from the United Arab Emirates. Epilepsy Res. 2020; 159:106259. doi: 10.1016/j.eplepsyres.2019.106259. Epub 2019 Dec 20. PMID: 31901526.
12. Mawhinney E, Craig J, Morrow J, Russell A, Smithson WH, Parsons L, *et al*. Levetiracetam in pregnancy: results from the UK and Ireland epilepsy and pregnancy registers. Neurology. 2013; 80(4):400-5. Doi: 10.1212/WNL.0b013e31827f0874. Epub 2013 Jan 9. Erratum in: Neurology. 2013; 80(7):691. PMID: 23303847.
13. Thomas SV, Syam U, Devi JS. Predictors of seizures during pregnancy in women with epilepsy. Epilepsia. 2012; 53(5):e85-8. doi: 10.1111/j.1528-1167.2012.03439.x. Epub 2012 Mar 16. PMID: 22429269.
14. Vajda FJE, Graham JE, Hitchcock AA, Lander CM, O'Brien TJ, Eadie MJ. Antiepileptic drugs and foetal malformation: analysis of 20 years of data in a pregnancy register. Seizure. 2019; 65:6-11. doi: 10.1016/j.seizure.2018.12.006. Epub 2018 Dec 19. PMID: 30593875.
15. Peller AJ, Westgate MN, Holmes LB. Trends in congenital malformations, 1974-1999: effect of prenatal diagnosis and elective termination. Obstet Gynecol. 2004; 104(5Pt 1):957-64. Doi: 10.1097/01.AOG.0000142718.53380.8f. PMID: 15516385.