ISSN: 2754-4923

Journal of Diagnosis & Case Reports

SCIENTIFIC Research and Community

Research Article

Open Access

Diagnosis of Pregnant Women with Seizures at Tikur Anbessa Hospital

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ABSTRACT

Information is yet scanty concerning current antiepileptic drugs prescribing patterns for women of childbearing age with epilepsy. Most women with epilepsy can give birth to perfectly healthy children after uneventful pregnancies. Best approach to management of epilepsy in pregnancy requires knowledge of the teratogenic effects of antiepileptic drugs, of the risks with uncontrolled seizures. Understanding the effects of pregnancy on seizure control and of gestational effects on antiepileptic drugs disposition is useful in early clinical diagnosis and patient management systems. We evaluated utilization of antiepileptic drugs among women of childbearing age against pre-set standards in epilepsy clinic of Tikur Anbessa Special and Referral Hospital from May 2017 to May 2018. The mean age of the women were 24.92± 6.54, where majority 217 (56.5%) of them aged between 15-25. Eighty-five (22.1%) of the women diagnosed with epilepsy were found to be pregnant, among them 20(5.2%) were breast-feeding. Generalized tonic clonic seizure (62.8%) was found to be the commonest seizure type diagnosed followed by unidentified or uncategorized seizures (16.7%), focal seizures (11.5%), and complex partial seizures (6.3%). Among the variety of anti-epileptic drug regimen or combinations used to treat epilepsy in 384 mothers, monotherapy 259 (67.4%) was the commonest drug regimen prescribed followed by dual therapy 97 (25.3%), and polytherapy 28 (7.3%). We here concluded that Valproic acid 44(51.8%) followed by phenytoin 36(42.4%) and phenobarbital 17(20%) were commonly given for breast-feeding women at Tikur Anbessa hospital.

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Received: January 09, 2021; **Accepted:** January 13, 2021; **Published:** January 23, 2021

Keywords: Epilepsy, Antiepileptic Drug's, Pregnant Women, Childbearing Age, Seizure

Introduction

Epilepsy is one of the most common neurological disorders, affecting about 50 million people worldwide [1]. Epilepsy is a chronic disorder characterized by recurrent seizures [2]. An approach to management of epilepsy in pregnancy requires knowledge of the teratogenic effects of antiepileptic drugs (AEDs), of the risks with uncontrolled seizures, and an understanding of the effects of pregnancy on seizure control of gestational effects on AEDs disposition [3]. Women taking AEDs have a greater risk of miscarriage and teratogenicity, including a 4–8% chance of giving birth to a child with major congenital malformations, because these agents can be transferred to the fetus via the placenta [4].

Around 90% of the people with epilepsy in developing countries are not receiving appropriate treatment due to cultural attitude, lack of prioritization, poor health system infrastructure as well as inadequate supply of AEDs. Economic factors are important determinants of clinical decision making & the degree of effect depends on the country's health systems strength. In developing countries, these may be more related to patients' ability to pay & that of availability of drugs [5, 6]. Criticisms of care (both primary and secondary) by women surveyed in a focus group discussion included poor provision of information about adverse effects, drug interactions with oral contraceptives, and perceived haphazard prescribing of AEDs resulting in serious adverse effects [7].

Based on the information of multiple pregnancy registries, consistent finding has emerged indicating that valproate poses an increased risk to the unborn child. This differential risk includes both anatomical and behavioural teratogenic defects, both of which are dose dependent. Overall risks for carbamazepine and lamotrigine exposure are low, but a risk for cleft lip/palate has been reported for both [8, 9]. From the time of diagnosis the important issues should therefore be considered, effects of AEDs on the developing embryo or fetus. AEDs are the mainstay of the therapy for epilepsy, despite the development in recent years of new therapeutic options, such as brain stimulation or surgery [10, 11].

Given the relatively few patients who can be managed with no pharmacological options. The primary goals of AEDs treatment are to achieve complete seizure freedom, ideally without adverse events, reduce morbidity and mortality, and improve quality of life [12]. Optimum AED therapy can abolish seizures in up to 70% of patients developing epilepsy, but in the remaining patient's remission is elusive [13]. Hormone-releasing intrauterine systems and other intrauterine contraceptive devices are apparently unaffected by enzyme inducers. Valproate, levetiracetam,

gabapentin, pregabalin, vigabatrin and zonisamide do not seem to affect hormonal contraception where lamotrigine has a minor effect on the norgestrel component reducing the levels by up to 20% [14].

All AEDs may be associated with teratogenicity [15]. Ideally the discussion about choice of AED treatment in girls and young women should always be made with future pregnancy in mind. Selection of AEDs is usually influenced largely by epilepsy syndrome. The studies on new AEDs suggest that lamotrigine is preferable to carbamazepine in the treatment of people with partial onset seizures, while valproate is both effective and generally well-tolerated in many patients with generalized and unclassified epilepsies. In women of childbearing age, however, other factors, particularly the risk of congenital abnormality in the unborn child, play a major part in the choice of AEDs [16].

The risks of obstetrical complications in pregnant women with epilepsy are uncertain but could include increased risk of caesarean delivery, preeclampsia, pregnancy-induced hypertension, pregnancy bleeding complications, premature contractions or premature labor and delivery, and spontaneous abortion [17]. European Surveillance of Congenital Anomalies (EUROCAT) study confirmed the risk for spina bifida for carbamazepine monotherapy (OR 2.6, 95% CI 1.2—5.3 compared with no AED exposure). The risk for carbamazepine did not differ from other AED monotherapies but was less than valproic acid. However, the risk of cleft lip/palate was not confirmed in the EUROCAT study [18].

Children exposed in utero to AED polytherapy had impaired verbal and nonverbal IQ compared with children exposed to monotherapy alone [19] If possible, AED polytherapy should be avoided to reduce the risk of poor cognitive and verbal outcomes [20]. Possible effects of prenatal AED exposure on neurodevelopment and behaviour have recently been analysed. In a population-based Danish study, national health care registries were used to identify exposure during pregnancy and neurodevelopmental disorders in the exposed children compared with unexposed children, maternal use of valproate was associated with a hazard ratio of 4.9 (95% CI 2.3–10.3) for childhood autism, and a ratio of 3.0 (95% CI 1.7–5.4) for autism spectrum disorder [21]. An analysis of IQ of 3-year-old children of mothers with AED-treated epilepsy showed no difference between those that had been breastfed compared with those that were not [22].

Monotherapy was commonly used in the management of seizure, 54.5%, among which phenobarbitone was the most commonly utilized single anticonvulsant drug. One hundred and sixty-five (56.7%) patients were seizure free during follow-up periods and 125 (43.3%) patients were not, of which 121 (73.3%) of patients had 1 up to 5 seizure attacks per 3 months during the 3 years follow-up period [23]. Another study in India shows that generalized tonic clonic seizures (GTCs) were most prominent followed by complex partial seizures. Most patients are young and epileptic seizures are more common in man. Polytherapy was most frequently used in all types of epileptic seizures. Sodium Valproate was the most frequently prescribed AED followed by Phenytoin sodium and Carbamazepine [24].

Prescribing of lamotrigine in pregnancy has steadily increased and has been the most popular AEDs prescribed in pregnancy since 2004. Pregnant women with epilepsy were twice as likely to stop receiving AEDs (Hazard Ratio (HR) 2.00, 95% Confidence Interval (CI) 1.62–2.47) when compared to non-pregnant women and for women with bipolar disorder this was even higher (HR 3.07, 95% CI 2.04–4.62). For pregnant women with epilepsy, those receiving AEDs less regularly before pregnancy were more likely to stop receiving AEDs in pregnancy [25].

Methods and Subjects

Hospital based retrospective cross sectional study was conducted at Tikur Anbessa Specialized Referral hospital from May 2017 to May 2018. It was carried out on 384 patients by systematic random sampling techniques. Data was collected from patient's medical records with AEDs prescribed and questionnaire interviews. Confidentiality of the information was maintained throughout by excluding names as identification of the participants. Ethical clearance was obtained from Addis Ababa University institutional review board department of neurology and Anatomy (IRB/SOM/05/17). Epileptic women of child bearing age (15-45) treated in epileptic clinic of Tikur Anbessa Specialized Referral Hospital during the study period were included. Patients with other central nervous system disorders like depression, schizophrenia, bipolar anxiety as well as unreadable medical card records were excluded. Data analysis and processing was done using SPSS version 20.0 and descriptive statistics was used to summarize categorical variables and X2 contingency analyses, where $p<0.005$ was considered as statistically significant.

Results

Among women(N=384) in the childbearing age included in this study, we show that the dominant age group was 15-25 years, followed by 26-35 years. Our study shows that 22.1% of women with epilepsy were pregnant and 5.2% of them were on the breast-feeding [Table 1].

Table 1: Baseline characteristics among epileptic women of childbearing age in Tikur Anbessa Specialized Hospital (N=384)

Characteristics		Number	Percentage
Age	**15-25**	**217**	**56.5**
	≥26-35	138	35.9
	≥36-45	29	7.6
Residence	**Addis Ababa**	**266**	**69.3**
	Oromia	80	20.8
	Amhara	6	1.6
	Southern Nations	29	7.6
	Dire Dawa	3	0.8
Pregnancy status	**Yes**	**85**	**22.1**
	No	299	77.9

Breast feeding status	**Yes**	**20**	**5.2**
	No	364	94.8
Number of children	1	47	12.2
	2	**68**	**17.7**
	3	10	2.6
	No children	259	67.4
N	**Total**	**384**	**100**

Among women(N=384) in the childbearing age included in this study, we found out that generalized tonic clonic seizure was the commonest seizure (62.8%) occurring among the pregnant women of childbearing age, followed by unidentified or uncategorized seizures (16.7%), focal seizures (11.5%) [Figure 1, Table 2].

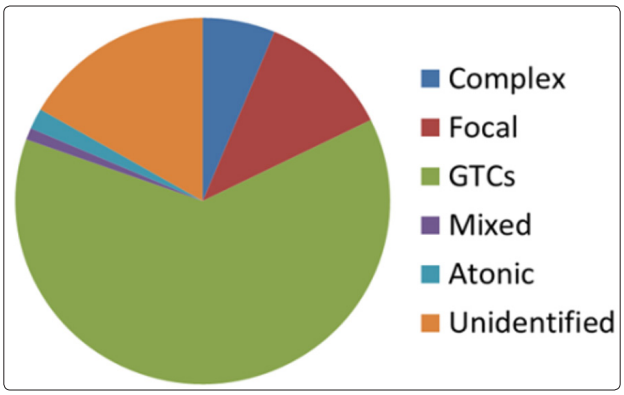

Figure 1: Types of seizure among epileptic women of childbearing age

Table 2: Frequency of antiepileptic therapy based on types of seizures among women of childbearing age

Drug therapy	Types of Seizure						Total (n=384)
	Complex	Focal	GTCs	Mixed	Atonic	Unidentified	
Mono therapy	5(20.8%)	37(84.1%)	163(67.6%)	0(0%)	5(71.4%)	49(76.6%)	259(67.4%)
Dual therapy	19(79.2%)	1(2.3%)	60(24.9%)	0(0%)	2(28.6%)	15(23.4%)	97(25.3%)
Poly therapy	0(0%)	6(13.6%)	18(7.5%)	4(100%)	0(0%)	0(0%)	28(7.3%)

Among women(N=384)in the childbearing age included in this study, we demonstrated that among the anti-epileptic drug regimen, monotherapy was the commonest drug regimen prescribed 67.4%, followed by dual therapy 25.3%, and polytherapy 7.3% [Figure 2,Table 3-5].

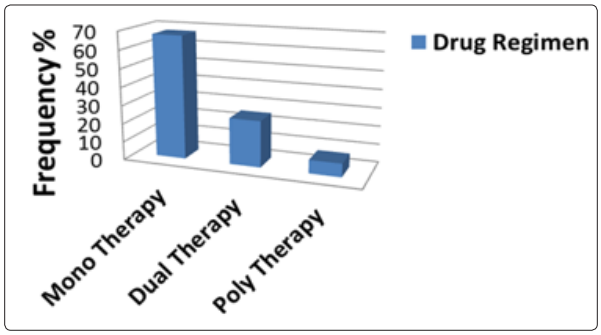

Figure 2: Frequency of antiepileptic drug therapy among women of childbearing age

Table 3: Distribution of antiepileptic drug therapy based on breast-feeding and pregnancy status among women of childbearing age

Antiepileptic drugs	Breast Feeding Status			Pregnancy Status			X^2
	Yes	No	Total	Yes	No	Total	
Mono therapy	0(0%)	259(71.2%)	259(67.4%)	73(85.9%)	186(62.2%)	259(67.4%)	p<0.001
Dual therapy	20(100%)	77(21.2%)	97(25.3%)	12(14.1%)	85(28.4%)	97(25.3%)	
Poly therapy	0(0%)	28(7.7%)	28(7.3%)	0(0%)	28(9.4%)	28(7.3%)	

Table 4: Categories of AEDs therapies based breast-feeding and pregnancy status among women of childbearing age

AED drugs		Mono therapy (N)	Dual therapy (N)	Poly therapy (N)	Total (N)
Carbamazepine	Yes	30 (65.2%)	6(13%)	10(21.7%)	46(100%)
	No	229(67.8%)	91(26.9%)	18(5.3%)	338(100%)
Phenytoin	Yes	77 (46.1%)	62(37.1%)	28(16.8%)	167(100%)
	No	182 (83.9%)	35(16.1%)	0(0%)	217(100%)
Phenobarbital	Yes	87(50.9%)	64(37.4%)	20(11.7%)	171(100%)
	No	172(80.8%)	33(15.5%)	8(3.8%)	213(100%)
Valproic acid	Yes	71(52.2%)	43(31.6%)	22(16.2%)	136(100%)
	No	188(75.8%)	54(21.8%)	6(2.4%)	248(100%)
Lamotrigine	Yes	1(7.7%)	10(76.9%)	2(15.4%)	13(100%)
	No	258(69.5%)	87(23.5%)	26(7.0%)	371(100%)
Clonazepam	Yes	0(0%)	0(0%)	1(100%)	1(100%)
	No	259(67.6%)	97(25.3%)	27(7%)	383(100%)

Table 5: Distribution of AEDs based on breast feeding status and pregnancy among women of childbearing age

AED drugs	Breast feeding status		
	Yes	No	Total
Carbamazepine	0(0%)	46(12%)	46(12%)
Phenytoin	10 (50%)	161(12%)	171(44.5%)
Phenobarbital	17 (20%)	154(51.5%)	171(44.5%)
Valproic acid	10 (50%)	126(34.6%)	136(35.4%)
Lamotrigine	10 (50%)	3(0.8%)	13(3.4%)
Clonazepam	0(0%)	1(0.3%)	1(0.3%)
AED drugs	Pregnancy status		
	Yes	No	Total
Carbamazepine	0(0%)	46(15.4%)	46(12%)
Phenytoin	36(42.4%)	131(43.8%)	167(43.5%)
Phenobarbital	17(20%)	154(51.5%)	171(44.5%)
Valproic acid	44(51.8%)	92(30.8%)	136(35.4%)
Lamotrigine	0(0%)	13(4.3%)	13(3.4%)
Clonazepam	0(0%)	1(0.3%)	1(0.3%)

Discussion

AEDs often are associated with teratogenicity. Indeed, the discussion about the choice of AEDs treatment in girls and young women should always be made with future pregnancy in mind. AEDs are also the mainstay of the therapy for epilepsy, despite the development of new therapeutic options in recent years, such as brain stimulation and /or surgery. The management of reproductive age group women with epilepsy is becoming of increasing importance as the risk factors for adverse outcomes of pregnancy; breastfeeding and infertility become more clearly delineated [1, 3, 4, 7]. Different anti-epileptic drug regimens or combinations treat epilepsy. Uncontrolled epilepsy in a pregnant woman is a serious and potentially life-threatening condition for both mother and child. Most pregnant women with epilepsy will need to take at least one antiepileptic drug. The goal for all concerned is a healthy, seizure-free mother and an undamaged child. Our finding was significantly higher than the study conducted in Bishoftu General Hospital [6, 8, 12, 14, 15, 23]. This might be due to the difference in sample size [Table 1]. Our study indicates that young and middle aged women characterized the study population, and that was why the lack of peak in the elderly was seen. Our study demonstrate that a generalized tonic clonic seizure (62.8%) was the commonly occurred in those women, followed by unidentified or uncategorized seizures (16.7%), focal seizures (11.5%)[Table 2].This finding is in agreement with the study conducted in Jimma University teaching hospital in Ethiopia. Uncategorized seizure which accounted about (16.7%) of the sample population might have been contributed due to lack of neuroimaging methods that can facilitate proper classification and diagnosis to the specific types of seizure in Ethiopian hospital settings.

Our finding show that monotherapy (67.4%) was the commonest drug regimen followed by dual therapy (25.3%) and the degree of polytherapy was (7.3%) [Table 3].This result was in line with study conducted in India, where majority of study population were prescribed an AED as monotherapy. Almost all of the polytherapy prescriptions consisted of triple therapy [22]. Phenobarbitals, Phenytoin, Valproic acid were the commonest drugs that were frequently administered as monotherapy and dual therapy. Lamotrigine and clonazepam were the least frequently used as monotherapy, dual therapy or polytherapy. This result was comparable to previous studies conducted in Jimma where phenobarbitone was the most frequently prescribed monotherapy, followed by phenytoin [16, 21, 22, 22, 25]. According to this

study Phenobarbital, Phenytoin, valproic acid and lamotrigine were commonly used to treat generalized tonic clonic seizure. Carbamazepine drug was administered for focal seizures. This is consistent with previous study conducted in Bishoftu general hospital [1, 9, 17, 19, 21].

Selection of AEDs is usually influenced largely by epilepsy syndrome. Compared with no pregnant women of childbearing age, pregnant women were non likely to be on AED monotherapy than polytherapy. Although this may be an attempt to avoid the risks of polytherapy during pregnancy, it may also reflect increased difficulty of conception in women on polytherapy because of the AEDs or the increased severity of epilepsy. AEDs are not recommended for pregnant women because they cross-placental barriers to the fetus and cause harm to babies. According to this finding, valproic acid (51.8%), phenytoin (42.4%) and phenobarbital (20%) were commonly given for pregnant women [Table 4]. This finding is in contrast with a study conducted in the United Kingdom where sodium valproate has declined since 1994 despite being the most commonly prescribed AEDs in pregnancy up to 2004. This difference might be due to lack of awareness about AEDs effect on pregnancy [23, 24, 25].

Majority of AEDs are not recommended for breast-feeding women because they pass to the child through breast milk and pose harm to the baby. According to this finding, valproic acid (50%), phenytoin (50%), lamotrigine (50%) and phenobarbital (20%) were commonly given for breast-feeding women (Table 5). This finding is in contrast with study done in Sweden where it stated that AED are transferred to the breast-milk; but in general, breast-fed infants are exposed to lesser amounts of AEDs through breast-feeding than they were in fetal life. Adverse effects are rare, although they might occasionally occur if mothers are treated with phenobarbital [1, 2, 3, 6]. Therefore, healthcare professionals need to keep up to date with the latest information on the risks of AEDs in pregnancy and breast-feeding, as they are harmful to fetus. There is lack of information on the relative risks between AEDs and common choice healthcare professionals and women have to make. The duration of therapy should be according to the standard guidelines and treatment to prevent under use and over use of AEDs. Research efforts in this area must continue in robust ways for inferences to be made and clearer guidance to be provided worldwide interventions.

Acknowledgments

We would like to thank Addis Ababa University, Tikur Anbessa Specialized Teaching Hospital for supporting us.

References

1. Rishe W, Seifu MF, Gelaw BK, Gunasekaran T, Tadesse E, et al. (2015) Drug use evaluation of antiepileptic drugs in outpatient epilepsy clinic of bishoftu general hospital , east shoa , ethiopia 4: 1516-1528.
2. Mathur S, Sen S, Ramesh L, M SK (2010) Utilization pattern of antiepileptic drugs and their adverse effects , in a teaching hospital 3: 55-59.
3. Tomson T (2013) Current anti-epileptic treatment in women of childbearing age 1: 195-200.
4. Veroniki AA, Cogo E, Rios P, Straus SE, Finkelstein Y, et al. (2017) Comparative safety of anti-epileptic drugs during pregnancy : a systematic review and network meta-analysis of congenital malformations and prenatal outcomes 2017: 1-20.
5. Cummings Ln, Giudice L MM (2005) Ovulatory Function In Epilepsy. Epilepsia 2005: 36.
6. Heaney Dc, Beran RG HM (2002) Economics in epilepsy treatment choices: our certain fate? Epilepsia 43: 532-538.
7. Wallace HK SJ (2009) Quality of epilepsy treatment and services: the views of women with epilepsy. Seizure 8: 81-87.
8. Chang S-I MJ (1998) Pharmacotherapeutic issues for women of childbearing age with epilepsy. Ann Pharmacother 32: 794-801.
9. Morrow JI, Russell A, Gutherie E, L Parsons, I Robertson, et al. (2006) Malformation risks of anti-epileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. J Neurol Neurosurg Psychiatry 77: 193-198.
10. Craig J, Campbell E. Epilepsy and women. In.
11. Theodore WH, R Fisher (2004) Brain stimulation for epilepsy. Lancet Neurol 3: 111-118.
12. Perucca E, Beghi E, Dulac O, S Shorvon, T Tomson (2000) Assessing risk to benefit ratio in antiepileptic drug therapy. Epilepsy Res 41: 107-139.
13. Brodie MJ KP (2001) The star systems: overview and use in determining antiepileptic drug choice. CNS Drugs 15: 1-12.
14. Baruzzi A, Fiorenzo Albani, Roberto Riva (1994) Oxcarbazepine: pharmacokinetic interactions and their clinical relevance. Epilepsia 1994: 35.
15. Marson AG, Al-Kharusi AM, Alwaidh M, Richard Appleton, Gus A Baker, et al. (2007) The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for the treatment of partial epilepsy: an unblinded randomised controlled trial 369: 1000-1015.
16. Marson AG, Al-Kharusi AM, Alwaidh M, Richard Appleton, Gus A Baker, et al. (2007) The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblended randomised controlled trial. Lancet 369: 1016-1026.
17. C L Harden, K J Meador, P B Pennell, W A Hauser, G S Gronseth, 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 Subcommittee of the Ame. Neurology 73: 133-141.
18. Jentink J, Bakker M K, Nijenhuis CM, B. Wilffert, Lolkje T.W. de Jong-van den Berg (2009) Dose folic acid use decreases the risk for spina bifida after in utero exposure to valproic acid. Pharmacoepidemiol Drug Saf 803-807.
19. Pennell PB (2008) Antiepileptic drugs during pregnancy: what is known and which AEDs seem to be safest?. Epilepsia 49: 43-55.
20. Koch S, Titze K, Zimmermann R B, M Schröder, Lehmkuhl U, et al. (1999) Long-term neuropsychological consequences of maternal epilepsy and anticonvulsant treatment during pregnancy for school-age children and adolescents. Epilepsia 40: 1237-1243.
21. Christensen J, Grønborg TK SM, Merete Juul Sørensen, Diana Schendel, Erik Thorlund Parner, et al. (2013) Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA 309: 1696-1703.
22. Meador KJ, Baker GA BN, N Browning, J Clayton-Smith, D T Combs-Cantrell, et al. (2010) NEAD Study Group. Effects of breastfeeding in children of women taking antiepileptic drugs. Neurology 75: 1954-1960.
23. Mesfin Gurshaw, Asrat Agalu, Tesfahun Chanie (2014) Anti-epileptic drug utilization and treatment outcome among epileptic patients on follow-up in a resource poor setting. Journal of young pharmacists 2014: 6.
24. Abhisek Pal, Shakti K Prusty, Pratap K Sahu, Truptirekha Swain (2011) Drug utilization pattern of antiepileptic drugs: a pharmacoepidemiologic and pharmacovigilance

study in a tertiary teaching hospital in India.Asian Journal of Pharmaceutical and Clinical Research 2011: 4.

25. Shuk-Li Man1, Irene Petersen, Mary Thompson, Irwin Nazareth (2012) Antiepileptic Drugs during Pregnancy in Primary Care: A UK Population Based Study.Plos ONE 7: 52339.