Epilepsy Research 149 (2019) 66–69

Contents lists available at ScienceDirect

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

Antiepileptic drug treatment during pregnancy and delivery in women with epilepsy—A retrospective single center study

Boris Shihman[a,b,1], Lilach Goldstein[a,b], Noam Amiel[a,b], Felix Benninger[a,b,*]

[a] Department of Neurology, Rabin Medical Center – Beilinson Hospital, Petach Tikva, Israel
[b] Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

ARTICLE INFO

Keywords:
Valproic acid
Antiepileptic drugs
Epilepsy
Pregnancy
Seizures
Teratogenicity

ABSTRACT

Purpose: Antiepileptic drugs (AED) are among the most common teratogenic drugs prescribed to women of childbearing age. During pregnancy, the risk of seizures has to be weight against the use of AED treatment. Primary goal was to observe and describe AED treatment policy and its changes during an eleven-year period at our third referral center.
Methods: We scrutinized the medical health records for all cases of female epileptic patients admitted for labor at the Rabin Medical Center during the years 2005 – 2015.
Results: A total of 296 deliveries were recorded with 136 labors occurring in the period 2005–2010 (22.7/y) and 160 in 2011–2015 (32.0/y; increase of 41%). Twelve different AEDs were prescribed to WWE during pregnancies in the 11-year period investigated (2005–2015). Most commonly used AEDs during pregnancy were Lamotrigine (36.1%), Carbamazepine (25.0%), and Valproic Acid (13.5%). Comparing their use during the years 2005–2010 and 2011–2015, Lamotrigine (35.3% vs. 36.9%) and Carbamazepine use (23.5% vs. 26.0%) increased slightly. Valproic acid use was markedly reduced in the second period: 18.4% in the years 2005–2010 lowered to 9.4% during 2011–2015, a reduction of 48%. Unfortunately, a trend towards an increase in treating WWE with more than one AED was observed.
Conclusions: The proportion of WWE treated with VPA during pregnancy was significantly reduced in the observed period (2005–2015). Change in fetal outcome during this period for WWE could not be detected.

1. Introduction

Epilepsy, the most common chronic neurological condition, affects 0.6%–1% of the population (Wiebe et al., 1999; Hauser et al., 1990) and 0.3% - 0.5% of pregnant women (Viinikainen et al., 2006). During pregnancy, WWE have an augmented risk of pregnancy-related complications and AED therapy is often continued to avoid an increase in seizure frequency (Razaz et al., 2017; Harden et al., 2009). Antiepileptic drugs (AED) are among the most common teratogenic drugs prescribed to women of childbearing age, and can induce both anatomical and behavioral teratogenicity (Tomson et al., 2011; Hill et al., 2014). The teratogenic risk is especially increased for valproic acid, high doses of AEDs, and combination therapies (Ban et al., 2015; Veroniki et al., 2017).

For valproate monotherapy, the risk of a major congenital malformation was 10.3% and was dose dependent (6.3% for doses lower than 650 mg/d, and 25.2% for doses higher than 1450 mg/d. (Tomson et al., 2018) Additionally, compared to women without epilepsy, epileptic seizures during pregnancy were independently associated with a 1.36-fold, 1.63-fold and 1.37- fold increased risk of low-birthweight infants, preterm delivery, and infants small for gestational age, respectively. The risk increased significantly for women with seizures during pregnancy compared to women with epilepsy without seizures during pregnancy (Veroniki et al., 2017; Tomson et al., 2015a, 2016). Additionally, findings suggest that women with epilepsy (WWE) are at a considerably heightened risk for many adverse outcomes during their delivery hospitalization, including a more than 10-fold increased risk of death (Veroniki et al., 2017; Nashef and Tomson, 2015; MacDonald et al., 2015). The benefit of preventing seizures by AED treatment during pregnancy has to be weighed against the teratogenic effects of AEDs. We herein describe the treatment policies at our epilepsy center for pregnant WWE over a period of eleven years, including modifications for AEDs.

2. Methods

We included all WWE who gave birth at the Department of Obstetrics and Gynecology, Rabin Medical Center, Campus Beilinson,

* Corresponding author at: Department of Neurology, Rabin Medical Center – Beilinson Hospital, Jabotinsky 35, 49100 Petach Tikva, Israel.
E-mail addresses: bscor2000@yahoo.com (B. Shihman), lilaclaytman@gmail.com (L. Goldstein), noam.am22@gmail.com (N. Amiel), felixbenninger@gmail.com, felixbe@clalit.org.il (F. Benninger).
[1] Current address: Assuta Kalaniot, 106 Menachem Begin Bd., Ashdod, Israel.

https://doi.org/10.1016/j.eplepsyres.2018.11.010
Received 11 August 2018; Received in revised form 25 September 2018; Accepted 20 November 2018
Available online 20 November 2018
0920-1211/

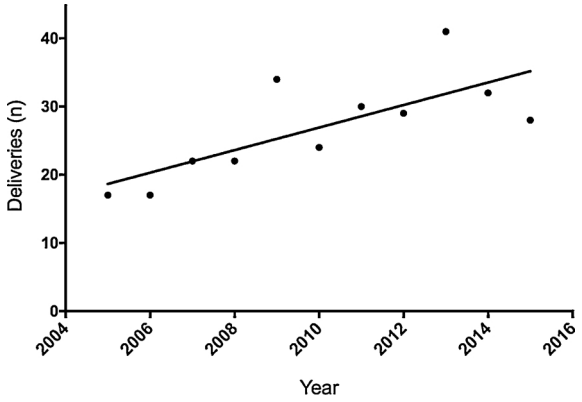

Fig. 1. Deliveries in WWE. Yearly increase in deliveries at our medical center of women with epilepsy (WWE).

Petach Tikva, Israel, during 2005-2015. The population was drawn from the local geographic region and included a significant proportion of patients with epilepsy in central Israel. Data was collected retrospectively and included 296 deliveries from 234 women (52 women with recurrent deliveries and 10 women with a third delivery during this period). The study population was derived from the hospital computerized database registrations of discharge diagnoses. Discharge diagnosis is coded at our institution according to the International Classification of Disease, ninth revision (ICD-9). The computerized database was screened for subcategory codes 780.39 (other convulsions), 780.33 (posttraumatic seizures) as well as category 345 including its subcategories. Diagnosis was confirmed by reviewing the individual patient files. Once patients were selected, doctors notes of individual patient files were screened for a diagnosis of diabetes mellitus, hypertension, depression or other psychiatric disorders mentioned during the time of pregnancy. Depression and other psychiatric disorders were not confirmed by a treating psychiatrist. Fetal outcome data was obtained from the patients discharge notes after delivery. The mean age of the women at time of the pregnancy was 31.3 ± 4.8 years (range: 20–56 years). Results were not corrected in regards to the contribution of multiple pregnancies by the same patients and all pregnancies were included equally.

Prism software (Graphpad, San Diego, CA) was used for statistical analysis. For calculating differences between two groups, we used either Student's *t*-test or Mann-Whitney-U Test. For multiple comparisons we used either one-way ANOVA or Kruskal-Wallis test. Pearson correlation coefficient was calculated for statistical assessment of changes over time. We set the significance level as smaller than 0.05 for all statistical calculations. The study was approved by the Rabin Medical Center local research ethics committee.

Table 1
Pregnancy complications in WWE (%).

	2005-2010	2011-2015	p-value
Hypertension	0.74	1.23	0.99
Preeclampsia	2.22	3.02	0.51
Diabetes	5.93	6.17	0.99
Hemorrhage	0.74	1.35	0.62

3. Results

3.1. Pregnancy increase in WWE (2005–2015)

At our center, the number of labors in WWE increased significantly by 41% from 2005 to 2010 (n = 22.7/y; total n_{6y} = 136) to 2011–2015 (n = 32.0/y; total n_{5y} = 160; p = 0.021). This linear increase of deliveries of WWE was steady (slope 1.65 ± 0.49; p = 0.0086) leading to a doubling of deliveries by 2015. (Fig. 1).

Mean age at delivery was 31.3 ± 4.8 years and did not differ significantly in the two periods (2005-1010: 30.8 years; 2011–2015: 31.7 years; p = 0.34). First ever delivery age was 28.8 ± 5.7 years (2005-1010: 29.2 years; 2011–2015: 28.4 years; p = 0.12). Interestingly, WWE at our center did not differ regarding age at delivery or first delivery relative to the general population (2015 Israel Central Bureau of Statistics www.cbs.gov.il; average delivery age: 30.3 years; average first delivery age: 27.6 years). Comparing both periods, no significant changes regarding the prevalence of diabetes mellitus or hypertension was noted in WWE during pregnancy (p = 0.54 and 0.72 respectively). There was a trend (although non-significant) of less comorbidity regarding depression (2005–2010: 5.2% and 2011–2015: 2.5%; p = 0.35) and other psychiatric disorders (2005–2010: 3.7% and 2011–2015: 1.2%; p = 0.17; see Table 1).

3.2. Monotherapy, polytherapy or no therapy

During pregnancy, 24.3% of WWE were not treated with AEDs throughout the investigated period (Fig. 2A and B). We found an obvious trend (not significant) towards WWE not being treated by AEDs during their pregnancies (2005–2010: 22.0%; 2011–2015: 26.2%; p = 0.69; r^2 = 0.16, p = 0.23). Just as the number of WWE not receiving AEDs during pregnancy increased, the fraction receiving more than one AED (polypharmacy) also tended to increase (2005–2010: 10.9%; 2011–2015: 13.3%; p = 0.30; r^2 = 0.08, p = 0.41) but did not reach significance. Consequently, monotherapy was on decline and only

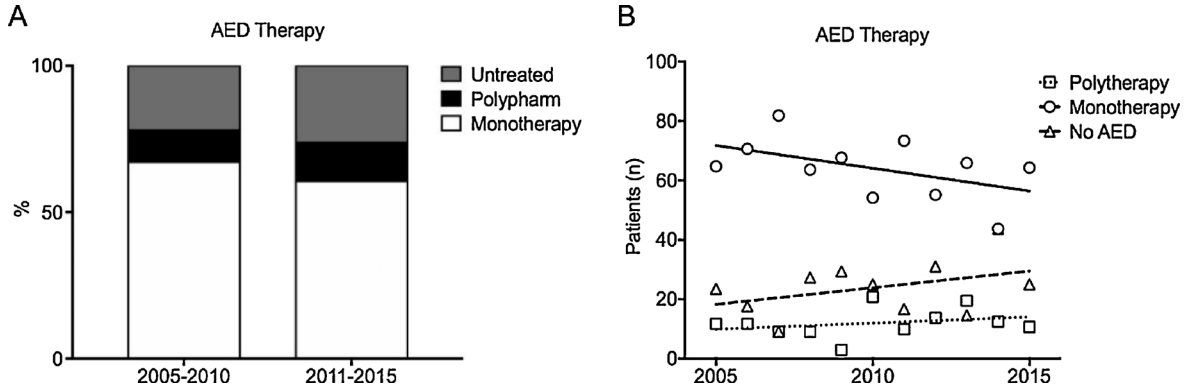

Fig. 2. Changes of AED treatment in WWE 2005-2015. Changes between the examined period regarding mono-, poly-therapy, or no therapy were non-significant (A; no AEDs: 2005–2010: 22.0%; 2011–2015: 26.2%; p = 0.69; poly-therapy: 2005–2010: 10.9%; 2011–2015: 13.3%; p = 0.30; monotherapy: 2005–2010: 67.1%; 2011–2015: 60.5%; p = 0.72). Increasing amounts of WWE trended not to be treated with AEDs during pregnancy or to use poly-therapy with a consequent reduction of monotherapy (B). Poly-therapy did not include the use of VPA.

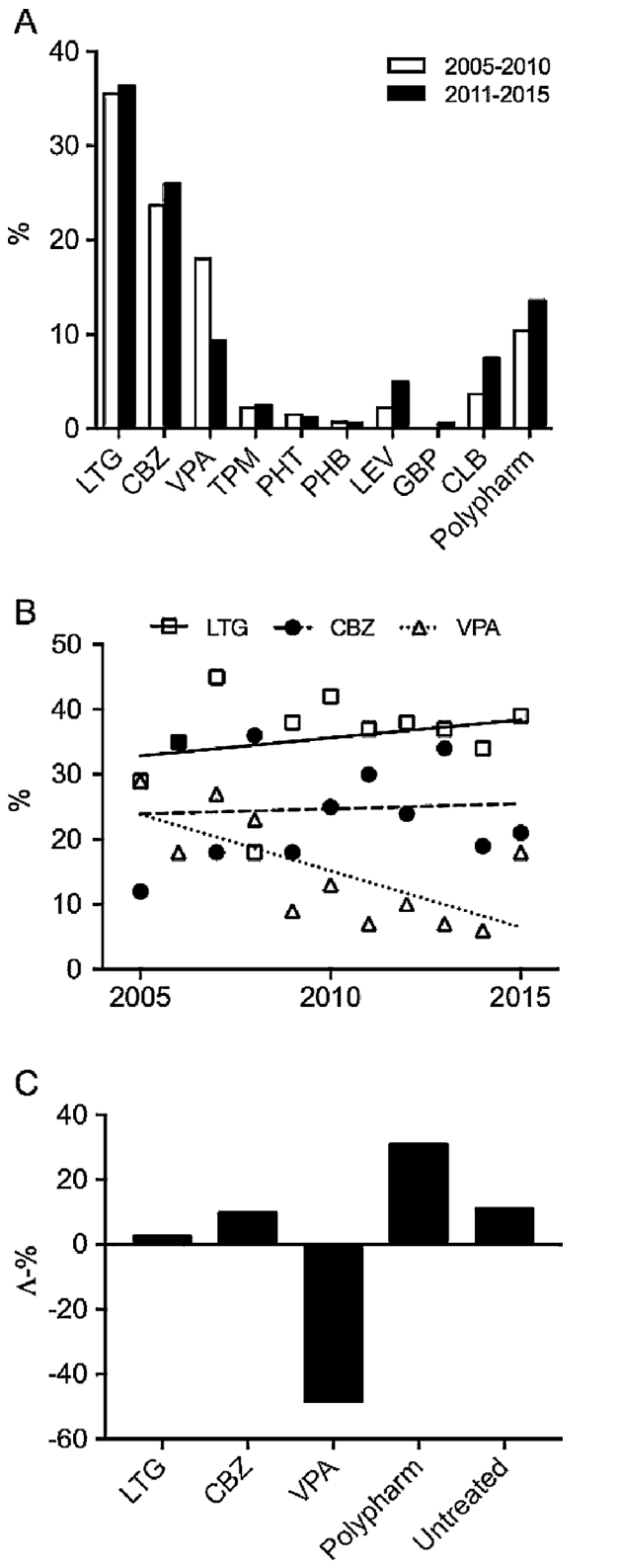

Fig. 3. Percentage of WWE using different AEDs as a comparison between the years 2005–2010 and 2011–2015 (A). The use of lamotrigine (LTG) and carbamazepine (CBZ) constantly increased in the time period analyzed. Valproic acid (VPA) use was reduced significantly in WWE during this period (B). Comparing the percentage change of use of lamotrigine (LTG), carbamazepine (CBZ), valproic acid (VPA), poly-therapy, and untreated patients between 2005–2010 and 2011–2015 (C).

Table 2
Fetal outcome in WWE (%). Poor fetal growth was defined as weight below the 10th percentile for gestational age. Excessive fetal growth was defined as weight above the 97th percentile for gestational age.

	2005-2010	2011-2015	p-value
Poor fetal growth	2.22	3.09	0.73
Excessive fetal growth	1.48	3.09	0.46
Fetal distress	6.67	9.88	0.40
Fetal abnormality	2.96	4.32	0.75

60.5% of WWE were treated with one single AED during pregnancy during 2011–2015, compared to 67.1% during 2005–2010 ($p = 0.72$; $r^2 = 0.25$, $p = 0.12$).

3.3. Anti-epileptic drug (AED) usage and change from 2005-2015

Twelve different AEDs were prescribed to WWE during pregnancies in the 11-year period investigated (2005–2015). These included Lamotrigine, Carbamazepine, Valproic Acid, Levetiracetam, Topiramate, Phenytoin, Oxcarbazepine, Phenobarbital, Gabapentin, Clonazepam, Clobazam, and Sultiam (Fig. 3A).

Most commonly used AEDs during pregnancy were Lamotrigine (36.1%), Carbamazepine (25.0%), and Valproic Acid (13.5%) (Fig. 3B). Comparing their use during the years 2005–2010 and 2011–2015, Lamotrigine (35.3% vs. 36.9%) and Carbamazepine use (23.5% vs. 26.0%) increased slightly. Valproic acid use was markedly reduced in the second period: 18.4% in the years 2005–2010 lowered to 9.4% during 2011–2015, a reduction of 48% ($p = 0.019$; Fig. 3C).

All other AEDs combined were used in 10.3% of WWE in the first period and their use increased to 17.5% in the second period. This was mainly due to an increased use of Levetiracetam (2.2% vs. 5.0%) and Clobazam (3.7% vs. 7.5%) as use of further AEDs did not change (Phenytoin: 1.5% vs. 1.2%; Phenobarbital: 0.7% vs. 0.6%; Gabapentin: 0.0% vs. 0.6%; Topiramate: 2.2% vs. 2.5%). See Fig. 3A.

3.4. Pregnancy, labor, delivery, and fetal outcome in WWE

Pregnancy complications in our cohort of WWE were similar during the two time periods analyzed (Table 1). Labor was considered preterm (less than 37 weeks of gestation) in 30 of the 297 (10.1%) deliveries and this did not differ significantly in the two periods investigated (2005–2010: 17/135; 12.6% and 2011–2015: 13/162; 8.0%; $p = 0.24$). Most deliveries in WWE were unassisted vaginal deliveries (78.8%; 2005–2010: 71.9% and 2011–2015: 69.8%; $p = 0.70$). Vacuum assisted deliveries occurred in 8.8% (2005–2010: 5.9% and 2011–2015: 9.9%; $p = 0.28$) of deliveries. Cesarean deliveries in WWE was unchanged in our cohort during the two periods (2005–2010: 22.2% and 2011–2015: 20.4% $p = 0.77$). Fetal outcome of pregnancy in WWE was very similar in both time periods regarding fetal growth, fetal distress during labor and fetal abnormalities (Table 2). While all fetal abnormalities in the first period (2005–2010) occurred in women treated with valproic acid, none of the fetal abnormalities in the second period were associated with its use. As minor fetal abnormalities we included fetal growth abnormalities or fetal distress. In the years 2011–2015, seven fetal abnormalities were found (7/162; 4.32%) whose mothers had been treated with different AEDs: 2 LTG, 2 CBZ, 1 LVT, and two on no AEDs.

4. Discussion

Epilepsy affects approximately 0.5–1% of women in childbearing age and is the most common serious neurological condition in pregnancy (Morrell, 2002; Hauser et al., 1993). Birth rates in WWE are

known to be significantly lower than in the general population. Low birth rates in WWE have been attributed to hormonal changes, psychosocial problems and the use of AEDs (Farmen et al., 2016; Wallace et al., 1998) The management of WWE during pregnancy is challenging regarding higher SUDEP and mortality rates (Edey et al., 2014), risk of seizures (Sveberg et al., 2015), perinatal complications and delivery (Razaz et al., 2017; Nashef and Tomson, 2015; Sveberg et al., 2015; Thomas et al., 2009; Viale et al., 2015), as well as teratogenicity of AEDs (Ban et al., 2015; Tomson et al., 2015a; Baker et al., 2015; Bank et al., 2017; Bromley and Baker, 2017). Our primary goal was to describe, retrospectively, changes in AED treatment policy over a period of eleven years at our tertiary referral center. 18]. The total numbers of deliveries of WWE increased at our center significantly, which might be due to an increasing population but can also be attributed to how we manage WWE at our hospital in a dedicated epilepsy outpatient clinic for WWE. Large prospective studies and registries (e.g. EURAP) compared several AEDs and their teratogenic risks (Razaz et al., 2017; Bromley and Baker, 2017; Weston et al., 2016; Tomson et al., 2015b).

The intrauterine first-trimester exposure to Valproic Acid has a higher risk of major congenital malformations compared with other AEDs and this effect is dose dependent; valproate should be avoided in the treatment of girls and women of childbearing potential. The risk seems to increase exponentially once several AEDs are prescribed (polytherapy) compared to one single AED (monotherapy) (Razaz et al., 2017; Tomson et al., 2015b). Unfortunately, the withdrawal of VPA during pregnancy has been associated with poorer seizure control (Tomson et al., 2016). In our retrospective cohort, the number of WWE treated with one AED was reduced over the course of the study period and a trend towards a larger percentage of WWE not being treated with AEDs during pregnancy was observed. Unfortunately, a trend towards an increase in treating WWE with more than one AED was observed. This might be due to the significant drop in the use of VPA in pregnant patients (reduction by 48%). Complication rates during the pregnancies did not change significantly when comparing the first and second half of the observed period. Even though the proportion of WWE treated with VPA during pregnancy was significantly reduced, fetal outcome was not improved. Fetal outcome was limited to structural findings and neurodevelopmental outcome was not assessed. Compared with multinational and multi-centered registries, our study is limited by the small number of patients included. Due to the small number of pregnancies, for many described observations, statistical significance could not be reached and conclusions can not be drawn. Further limitations include the fact that multiple pregnancies by the same patient were treated equally and included in the study. This lack of correction can lead to a possible distortion of the results. Additionally, the mentioned diagnoses of depression or other psychiatric diseases were not confirmed by a treating psychiatrist. The assessment of a treating general physician or neurologist regarding these additional diagnoses might be inaccurate.

In conclusion, deliveries by WWE in our hospital increased during 2005-2015. We found a marked decline in the use of VPA during pregnancies (-48%) accompanied with an increase in the use of multiple AEDs (~20%). Our retrospective single center study was underpowered to detect any change in delivery or fetal outcome related to the observed marked reduction in the use of Valproic Acid in WWE during pregnancy.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

None of the authors has any conflict of interest to disclose.

References

Wiebe, S., Bellhouse, D.R., Fallahay, C., Eliasziw, M., 1999. Burden of epilepsy: the ontario health survey. Can. J. Neurol. Sci. 26 (November (4)), 263–270.
Hauser, W.A., Hesdorffer, D.C., Epilepsy Foundation of America, 1990. Epilepsy. Demos Medical Pub 1 p.
Viinikainen, K., Heinonen, S., Eriksson, K., Kalviainen, R., 2006. Community-based, prospective, controlled study of obstetric and neonatal outcome of 179 pregnancies in women with epilepsy. Epilepsia 47 (January (1)), 186–192 Blackwell Science Inc.
Razaz, N., Tomson, T., Wikström, A.-K., Cnattingius, S., 2017. Association Between Pregnancy and Perinatal Outcomes Among Women With Epilepsy. JAMA Neurol. 74 (August (8)), 983–989.
Harden, C.L., Hopp, J., Ting, T.Y., Pennell, P.B., French, J.A., Hauser, W.A., 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, vol. 73. Lippincott Williams & Wilkins, pp. 126–132 Neurology.
Tomson, T., Battino, D., Bonizzoni, E., Craig, J., Lindhout, D., Sabers, A., 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 (July (7)), 609–617 Elsevier.
Hill, D.S., Wlodarczyk, B.J., Palacios, A.M., Finnell, R.H., 2014. Teratogenic effects of antiepileptic drugs. Expert Rev. Neurother. 10 (January (6)), 943–959.
Ban, L., Fleming, K.M., Doyle, P., Smeeth, L., Hubbard, R.B., Fiaschi, L., et al., 2015. Congenital anomalies in children of mothers taking antiepileptic drugs with and without periconceptional high dose folic acid use: a population-based cohort study. PLoS One 10 (July (7)) Räisänen SH e0131130–15.
Veroniki, A.A., Cogo, E., Rios, P., Straus, S.E., Finkelstein, Y., Kealey, R., et al., 2017. Comparative safety of anti-epileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes. BMC Med. (May (2)), 1–20.
Tomson, T., Battino, D., Bonizzoni, E., Craig, J., Lindhout, D., Perucca, E., et al., 2018. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. Lancet Neurol. 17 (June (6)), 530–538.
Tomson, T., Xue, H., Battino, D., 2015a. Major congenital malformations in children of women with epilepsy. Seizure: Eur. J. Epilepsy (March (14)), 1–5 BEA Trading Ltd.
Tomson, T., Battino, D., Bonizzoni, E., Craig, J., Lindhout, D., Perucca, E., et al., 2016. Withdrawal of valproic acid treatment during pregnancy and seizure outcome: observations from EURAP. Epilepsia 57 (June (8)) e173–7.
Nashef, L., Tomson, T., 2015. Epilepsy: intriguing new data on epilepsy and risks at delivery. Nat. Rev. Neurol. 11 (September (10)), 550–552 Nature Publishing Group.
MacDonald, S.C., Bateman, B.T., McElrath, T.F., Hernández-Díaz, S., 2015. Mortality and Morbidity During Delivery Hospitalization Among Pregnant Women With Epilepsy in the United States. JAMA Neurol. 72 (September (9)), 981–988.
Morrell, M.J., 2002. Epilepsy in women. Am. Fam. Phys. 66 (October (8)), 1489–1494.
Hauser, W.A., Annegers, J.F., Kurland, L.T., 1993. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Epilepsia 34 (May (3)), 453–468.
Farmen, A.H., Grundt, J.H., Tomson, T., Nakken, K.O., Nakling, J., Mowinchel, P., et al., 2016. Age-specific birth rates in women with epilepsy: a population-based study. Brain Behav. 6 (June (8)) e00492–5.
Wallace, H., Shorvon, S., Tallis, R., 1998. Age-specific incidence and prevalence rates of treated epilepsy in an unselected population of 2,052,922 and age-specific fertility rates of women with epilepsy. Lancet 352 (December (9145)), 1970–1973.
Edey S., Moran N., Nashef L. SUDEP and epilepsy-related mortality in pregnancy. Epilepsia 1st ed. Wiley/Blackwell (10.1111); 2014 Jul;55(7):e72–4.
Sveberg, L., Svalheim, S., Taubøll, E., 2015. The impact of seizures on pregnancy and delivery. Seizure: Eur. J. Epilepsy 1 (May (28)), 35–38 BEA Trading Ltd.
Thomas, S.V., Sindhu, K., Ajaykumar, B., Devi, P.B.S., Sujamol, J., 2009. Maternal and obstetric outcome of women with epilepsy. Seizure 18 (April (3)), 163–166.
Viale, L., Allotey, J., Cheong-See, F., Arroyo-Manzano, D., Mccorry, D., Bagary, M., et al., 2015. Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis. Lancet 386 (November (10006)), 1845–1852.
Baker, G.A., Bromley, R.L., Briggs, M., Cheyne, C.P., Cohen, M.J., García-Fiñana, M., et al., 2015. IQ at 6 years after in utero exposure to antiepileptic drugs: a controlled cohort study. Neurology 84 (January (4)), 382–390.
Bank, A.M., Stowe, Z.N., Newport, D.J., Ritchie, J.C., Pennell, P.B., 2017. Placental passage of antiepileptic drugs at delivery and neonatal outcomes. Epilepsia 58 (April (5)) e82–6.
Bromley, R.L., Baker, G.A., 2017. Fetal antiepileptic drug exposure and cognitive outcomes. Seizure: Eur. J. Epilepsy 44 (January (44)), 225–231 BEA Trading Ltd.
Weston J., Bromley R., Jackson C.F., Adab N., Clayton-Smith J., Greenhalgh J., et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Epilepsy Group, editor. Cochrane Database of Systematic Reviews 2016 Nov 7;8(1):26–355.
Tomson, T., Battino, D., Bonizzoni, E., Craig, J., Lindhout, D., Perucca, E., et al., 2015b. Dose-dependent teratogenicity of valproate in mono- and polytherapy. Neurology 85 (September (10)), 866–872.