Alma Mater Studiorum – Università di Bologna

DOTTORATO DI RICERCA IN

Scienze Mediche Specialistiche

Ciclo XXVII

Settore Concorsuale di afferenza: 06/D6

Settore Scientifico disciplinare: MED/26

TITOLO

ANTIEPILEPTIC DRUGS AND PREGNANCY. POPULATION BASED PHARMACO-EPIDEMIOLOGICAL STUDY ON PRESCRIPTION PATTERNS, PREGNANCY OUTCOME AND FOETAL HEALTH

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Esame finale anno 2015

ABSTRACT

Aims of the study: To assess the prevalence of Antiepileptic Drug (AED) exposure in pregnant women with or without epilepsy and the comparative risk of terminations of pregnancy (TOPs), spontaneous abortions, stillbirth, major congenital malformations (MCMs) and foetal growth retardation (FGR) following intrauterine AED exposure in the Emilia Romagna region (RER), Northern Italy (4 million inhabitants).

Methods: Data were obtained from official regional registries: Certificate of Delivery Assistance, Hospital Discharge Card, reimbursed prescription databases and Registry of Congenital Malformations. We identified all the deliveries, hospitalized abortions and MCMs occurred between January 2009 and December 2011.

Results: We identified 145,243 pregnancies: 111,284 deliveries (112,845 live births and 279 stillbirths), 16408 spontaneous abortions and 17551 TOPs. Six hundred and eleven pregnancies (0.42% 95% CI: 0.39-0.46) were exposed to AEDs. Twenty-one per cent of pregnancies ended in TOP in the AED group vs 12% in the non-exposed (OR:2.24; CI 1.41-3.56). The rate of spontaneous abortions and stillbirth was comparable in the two groups. Three hundred fifty-three babies (0.31%, 95% CI: 0.28-0.35) were exposed to AEDs during the first trimester. The rate of MCMs was 2.3% in the AED group (2.2% in babies exposed to monotherapy and 3.1% in babies exposed to polytherapy) vs 2.0% in the non-exposed. The risk of FGR was 12.7 % in the exposed group compared to 10% in the non-exposed.

Discussion and Conclusion: The prevalence of AED exposure in pregnancy in the RER was 0.42%. The rate of MCMs in children exposed to AEDs in utero was almost superimposable to the one of the non-exposed, however polytherapy carried a slightly increased risk . The rate of TOPs was significantly higher in the exposed women. Further studies are needed to clarify whether this high rate reflects a higher rate of MCMs detected prenatally or other more elusive reasons.

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1. BACKGROUND

Epilepsy is a chronic condition affecting 0.3-0.8% of pregnant women in developed countries (Olafsson et al., 1998; Richmond et al., 2004; Viinikainen et al., 2006; Borthen et al., 2011).

Most patients require long-term therapy with antiepileptic drugs (AEDs) that cannot be suspended during pregnancy due to the potentially adverse effects of seizures on women and their offspring. Seizures, especially if tonic-clonic, can lead to severe injury and even death. A recent report of the United Kingdom Confidential Enquiries into Maternal Deaths showed that, in the triennium 2006-2008, 5.4% of the deaths during pregnancy or puerperium were epilepsy-related (CMACE 2011; Edey et al, Epilepsia 2014). Moreover, several reports raise concern about a possible detrimental effect of maternal generalized tonic-clonic seizures (GTCS) on the foetus. Teramo et al. described two cases in which foetal heart rate was recorded during a maternal epileptic seizure during labour, showing in both a pattern of bradycardia followed by decreased short-term and long-term variability, with clear fetal asphyxia in the most severe case. It was postulated that the increase in intrauterine pressure during a seizure might decrease the uteroplacental blood flow. (Teramo et al., 1979). A case of fetal intracranial hemorrhage after a maternal seizure was also reported (Minkoff H et al., 1985). Traumatic foetal injury after maternal seizures and foetal loss after a GTCS-status were also described (EURAP Study Group, 2006).

Women without epilepsy may also be exposed to antiepileptic drugs (AEDs) during pregnancy, as these drugs are increasingly used for other diseases, among which bipolar mood disorder, migraine and neuropathic pain (See Appendix 2. AEDs indications other than epilepsy). Besides, most women with bipolar disorder should not even discontinue therapy during pregnancy, as this can raise the risk of relapse of more than twofold (Viguera et al., 2007).

Accordingly, the prevalence of AED use in pregnant women is 0.2% to 2.2% and it shows an increasing trend in some studies (Czeizel et al., 1992; Malm et al., 2003; Wide et al., 2004; Bobo et al., 2012; Kilic et al., 2014; Wen et al., 2015).

Exposure to older generation AEDs, such as phenobarbital (PB), phenytoin (PHT), valproate (VPA) and carbamazepine (CBZ), during the first trimester of pregnancy, the period of organogenesis, has been consistently associated with an approximately 2- to 3-fold increased risk of major congenital malformations (MCMs): 4-10% vs 2-5% in the general population (Perucca, 2005). Malformation rates associated with a specific AED vary considerably between studies, depending on population and methodological approaches.

However, VPA, compared to other AEDs, was almost invariably associated with a higher incidence of MCMs, varying between 4.7% and 54.5%, in a dose-dependent manner (Wide et al., 2004; Perucca, 2005; Vajda et al., 2005; Wyszynski et al., 2005; Morrow et al., 2006; Meador et al., 2008; Cunnington et al., 2011; Holmes et al., 2011; Tomson et el., 2011;

Campbell et al., 2014; Vajda et al., 2014). In particular, VPA use has been associated with spina bifida, hypospadia, atrial septal defect, polydactily, cleft palate and craniosynostosis (Jentik et al., 2010a).

PHT was the first AED in which teratogenicity was noted and a specific “fetal hydantoine syndrome”, including facial dysmorphism, mental retardation and delayed intrauterine growth was recognized (Loughnan et al., 1973, Hanson et al., 1975); subsequent studies reported variable incidence (0.7-9.1%) of MCMs in women exposed to PHT (Canger et al., 1999;Perucca 2005; Hernandez-Diaz et al., 2012), which however is currently little used in women of childbearing age.

Early studies did not consider PB as a highly teratogenic medication, although a relative specific risk of cardiac defects and facial clefts was reported (Samren et al. ,1999), whereas newer studies found an increased risk of MCMs overall, with an incidence ranging from 4.9% to 7.4 % (Holmes et al., 2001; Holmes et al., 2004; Meador, et al. 2008; Tomson et al., 2011; Hernandez-Diaz et al., 2012; Tomson and Battino 2012).

CBZ has been associated with spina bifida with a 5-fold higher risk than the general population, as well as orofacial clefts, hypospadia and heart defects; however it is considered less teratogenic than the other older AEDs, with an overall incidence of MCMs comprised between 1.9 and 7.3% in various studies (Rosa et al., 1991; Jentink et al., 2010b; Tomson et al., 2011; Hernandez-Diaz et al., 2012; Campbell et al., 2014).

Since the 1990s, several newer AEDs have been licensed; their use has been constantly increasing and, being considered safer, some of them, and namely lamotrigine (LTG) and levetiracetam (LEV), are currently the most used AEDs in women of childbearing age (Meador et al., 2009) and during pregnancy in developed countries (Moolgard-Nielsen and Hviid, 2011; Wen et al., 2015).

LTG has been associated with craniofacial defects, particularly cleft palate, in some studies (Vajda et al., 2005; Morrow et al., 2006; Holmes et al., 2008a) but not in others (Dolk et al., 2008; Cunnington et al., 2011). The overall risk of MCMs with LTG in monotherapy varies between 1.8 and 5.4 % and it is dose-dependent (Cunnington et al., 2011; Tomson et al., 2011; Hernandez-Diaz et al., 2012; Campbell et al.,2014).

Data have been accumulating on levetiracetam and, so far, there is no evidence of teratogenicity for this drug in monotherapy (Artama et al., 2005; Montouris et al., 2005; Morrow et al., 2006; Hunt et al., 2006 ; Holmes et al., 2008; Molgaard-Nielsen and Hviid, 2011; Tomson et la., 2011; Mawhinney et al., 2013; Chauhdry et al., 2014; Vajida et al. 2014).

Recent studies reported an increased risk of MCMs after topiramate (TPM) exposure during pregnancy, ranging from 2.4% to 6.9%, and in particular of cleft palate, which showed an incidence of more than 10 times the background, and hypospadia. TPM teratogenicity seems to be enhanced in polytherapy with other AEDs (Hunt et al., 2008; Moolgard-Nielsen and Hviid, 2011; Tomson et al., 2011; Hernandez-Diaz et al., 2012; Margulis et al., 2012; Mines et al., 2014).

Oxcarbazepine and gabapentin have not been associated with a significant higher risk of MCMs in monotherapy but caution is needed in interpreting published data, due to the low number of women exposed in monotherapy (Montouris et al., 2005; Morrow et al., 2006; Molgaard-Nielsen and Hviid, 2011; Tomson et al., 2011; Hernandez-Diaz et al., 2012; Fuji et al., 2013; Guttuso et al., 2014; Veiby et al., 2014).

Published data on the teratogenicity of vigabatrin, felbamate, zonisamide, pregabalin, rufinamide, lacosamide, retigabine and tiagabine are scanty or absent.

The risk of MCMs appears to increase with polytherapy, especially if containing VPA (Morrow et al., 2006). Indeed, recent studies showed an increased risk rate of LTG and CBZ in polytherapy compared to monotherapy only when VPA was included (Cunnington et al., 2011; Holmes et al., 2011).

Rates of MCMs increase with increasing dosages of the drugs and this is particularly the case with VPA (Morrow et al., 2006; Tomson et al, 2011; Hernandez-Diaz S et al., 2012; Campbell et al.,2014). It has been suggested that incidence of MCMs associated with a low dose of a higher-risk drug might be comparable to that associated with a high dose of a lower-risk drug, which may have a major clinical impact when seizures are not controlled by one of the latter. (Morrow et al.2006; Tomson et al., 2011).

Although some studies found an increased prevalence of MCMs in children born to untreated women with epilepsy (WWE) (Morrow et al., 2006) a comprehensive review of the literature and more recent studies do not support the hypotheses of an association between epilepsy per se and a major increase in the risk of MCMs (Holmes et al., 2001; Fried S et al., 2004). In addition, a recent large study did not find an association between epilepsy type or generalized tonic-clonic seizures in the first trimester and MCMs risk (Tomson et al., 2011).

Parental history of MCMs was related to a 4-fold higher risk (Tomson et al., 2011). In one study, the risk of having a child with an MCM was higher in women who have had another child with an MCM while on AEDs (Campbell et al., 2013). This was not confirmed in another study (Begum et al., 2013).

Folate intake during preconception and first trimester of pregnancy might reduce the risk of neural tube, cardiovascular and urinary tract defects and oral clefts in infants born to healthy women (MRC Vitamin Study Research Group, 1991; Berry et al.,1999) and folates at the dose of 400 mcg per day are recommended in all women planning a pregnancy. For women using AEDs which are disruptors of folate metabolism (i.e., PB, CBZ, PHT, primidone, and, to a lesser extent, LTG) or carry an increased risk for spina bifida (i.e. VPA, CBZ), the routinely recommended dose could be insufficient and it has been suggested that a dose of at least 4 mg per day should be prescribed (Wilson et al., 2003). However, whether folate intake reduces the risk of MCMs in infants born to women taking AEDs remains unclear and several studies failed to find any protective effect (Yerby et al., 2003; Tomson et al., 2011).

Until recent times studies on AEDs use in pregnancy have focused mainly on the risk of MCMs, and less is known on other possible adverse foetal outcomes.

A systematic review found no evidence of an increased risk of spontaneous abortion in WWE (Harden et al., 2009) and this was confirmed in a recent population-based study (Bech et al., 2014).
Data on stillbirths in WWE are conflicting: it was reported both that their incidence was comparable to that of the general population (Olafsson et al., 1998) and that they were up to twice as common (Waters et al. 1994, Richmond et al., 2004).
In a recent population study preterm deliveries were more common in women using AEDs, but only for indications other than epilepsy (Killic et al., 2014).
A systematic review of the literature and several subsequent studies showed that fetal growth retardation and the risk of being small for gestational age are more common in women taking AEDs (Hvas et al., 2000; Artama et al., 2013;Killic et al.; 2014 Veiby et al. 2014), while a cohort study claimed that the risk could be increased on polytherapy but not on monotherapy (Wide et al., 2000) and other studies did not report an increased frequency (Lin et al., 2009; Mawer et al., 2010).
A recent retrospective Brazilian study showed a greater incidence of mortality and hemorrhagic disorder in newborns exposed to AEDs in utero. However 70% of the babies were exposed to PB which, being an enzyme-inducer, interferes with the metabolism of vitamin K (Barroso et al., 2014). In Italy all newborns routinely receive vitamin K at delivery, and at present no further measures are advised in neonates exposed to AEDs (Harden et al., 2009).
The number of cesarean sections among WWE did not differ from the controls in a study, while it was increased up to 2-fold in others (Olafsson et al., 1998; Borthen et al., 2010; Borthen et al., 2011).
Little is known on the relevance of the clinical indication for AEDs to the fetal outcome. In addition to the observations on untreated WWE and to the mentioned study by Killic et al., it is worth mentioning a recent Swedish population based study, showing that bipolar mood disorder per se, irrespective of therapy, increases the risk of planned cesarean delivery, preterm birth, microcephalia, small for gestational age infants, neonatal hypoglicemia (Boden et al., 2012).

Until the 1990s, data on AEDs teratogenicity were sparse and relied mainly on underpowered observational studies. In fact, due to the low risk of specific MCMs, observational studies require very large numbers of patients to obtain reliable data. Currently the main sources of data on AEDs safety in pregnancy are pregnancy registries, some conducted by the pharmaceutical industry, some by independent healthcare professionals. Although registry-based studies considerably increased the information on the topic, they have several limitations. Many of them enrol only WWE, excluding women taking AEDs for other disorders and most studies have voluntary enrolment which may introduce selection biases towards high risk or low risk populations. Some studies include only patients from epilepsy centres, who could have more severe forms of epilepsy and thus a more aggressive treatment regimen. This may introduce a bias towards higher risk or, on the contrary, a more rational treatment regimen could introduce a bias towards lower risk. Some registries exclude women who already have some knowledge of foetal status, including possible MCMs, having undergone ultrasound at 16-20 weeks of gestation, thus possibly

underestimating MCMs rates. Data collection from many different investigators is difficult to standardize in large multicentric studies. Some registries have a considerable loss to follow-up rate, and most lack of information on adverse outcomes other than major MCMs, including pregnancy losses and stillbirth. Finally, many studies lack of comparison with an unexposed population.

A large population-based study can address many of these limits yielding information on pregnancy outcomes in the whole population of pregnant women, exposed and unexposed to AEDs.

The Emilia Romagna Region (RER) collects data on deliveries, abortions, MCMs and drug prescriptions in official registries: Certificate of Delivery Assistance registry (CedAP); Hospital Discharge Card (SDO) registry (ICD codes related to pregnancy and abortion); databases of all the reimbursed prescriptions in RER: AFT (prescriptions supplied by private pharmacies), DD (prescriptions supplied by hospital pharmacies to outpatients) and DPC (prescriptions supplied by private pharmacies on behalf of hospital pharmacies) and the Emilia Romagna birth defects register (IMER). Data from the different registries are available and can be linked.

AIMS

Primary aims of the study were:

1) to assess the prevalence of AEDs exposure during pregnancy (any stage) in women with and without epilepsy in the RER;

2) to describe the AEDs prescription patterns in pregnant women with and without epilepsy;

3) to determine the incidence and comparative risk of MCMs following AEDs monotherapy or polytherapy during the first trimester of pregnancy.

Secondary aims were:

1) to determine the incidence and comparative risk of MCMs following the intake of any specific AED during the first trimester of pregnancy;

2) to determine the incidence and comparative risk of specific MCMs following AEDs monotherapy or polytherapy during the first trimester of pregnancy;

3) to determine the incidence and comparative risk of MCMs overall and the specific risk of MCMs in infants born to WWE exposed to any AED on monotherapy and polytherapy during the first trimester of pregnancy;

4) to determine the incidence and comparative risk of foetal growth retardation (FGR), stillbirth, spontaneous and induced abortions in women exposed to AEDs during pregnancy;

5) to create a permanent surveillance system of pregnancy outcomes in women taking AEDs in the RER.

3. METHODS

3.1 Local ethical committee approval

The study started after approval of the Local Ethical Committee, obtained on 21/2/2013 and Hospital Health Direction (Direzione Sanitaria) authorization (determination 464, 13/3/2013).

3.2 Preliminary study: identification of AEDs prescription patterns in women with and without epilepsy

This step of the study was designed to identify prescription patterns allowing us to discriminate women using AEDs according to the clinical indication: epilepsy or other diseases. Most indications are very unlikely in pregnancy either because very rare in young women (i.e. essential tremor) or because they allow a withdrawal in pregnancy (i.e. prophylaxis of migraine). Therefore we considered, as alternative to epilepsy, only psychiatric disturbances, conditions in which the therapy is generally maintained.

3.2.1 Population: Women referring to the Bologna Health Trust (380.181 inhabitants in 2010), aged 18 - 45 years who for a six-month period comprised between the 1st of January and the 30th of June 2010 or 2011:

– had an established diagnosis of epilepsy and underwent at least one visit at the Epilepsy Centre of the ISNB of Bologna (Epilepsy cohort: EPI)

Or

-had an established diagnosis of psychiatric disorder, and underwent at least one visit at the Mental Health Department, Bologna Health Trust; women with a concomitant diagnosis of epilepsy were excluded (Psychiatric disorders cohort: PSY)

And

- had at least two prescriptions of AEDs (ATC - the Anatomical Therapeutic Chemical Classification system- code: N03A) (www.whocc.no) during the first semester of 2010 or 2011.

3.2.2 Recruitment

A maximum number of 100 clinical charts for each cohort were consecutively selected from the archives of the Epilepsy Centre of the ISNB of Bologna and of the Mental Health Department, Bologna Health Trust. Charts were manually screened, starting from those recorded for the first time in 2011 and going backward in time, until the final number was reached or until screening of the whole archive.

3.2.3 Prescription data sources

Data on the reimbursed prescriptions of the selected women were obtained from two pharmaceutical regional databases: Sistema Informativo Territoriale (SIT) and Assistenza Farmaceutica Territoriale (AFT).

3.2.4 Collection of data

The following data were collected:

Active substance: Substances classified as AEDs (ATC code N03A), antipsychotics (ATC code N05A), lithium (ATC code N05AN01) and antidepressants (ATC code N06A) were considered.

Average daily dose: It was calculated as the ratio between the total dose and the observation period

Intensity of treatment: It was expressed as the ratio between the average daily dose and the Daily Defined Dose (DDD). The DDD is a standardized unit of measure, established by the World Health Organization (WHO), defined as the assumed average maintenance dose per day for a drug used for its main indication in adults in monotherapy. It is commonly used in pharmaco-utilization studies as it allows comparisons among different populations and periods of observation.

3.2.5 Statistical analysis

Creation of a classification tree: We used a hierarchical classification model to group women according to the type of disorder: epilepsy or psychiatric disorder. The goal was to predict which women can be successfully allocate to the disorder group on the basis of the following clinical information: number of AEDs, number of antidepressants, number of antipsychotics, 42 single active substances belonging to those classes, intensity of treatment . The classification model was built using the rpart package (version 4.1-8) in R version 3.0.3. This approach selects a hierarchical sequence of partitions in which the split that maximizes the improvement of predictive power is chosen at every step. In order to avoid an over fitting of the data we selected a tree size after inspection of the relative error of each size.

The classification tree was estimated using data (training data set) of the two cohorts of women. We measured the performance of the model in the training dataset by the error rate: percentage of women incorrectly classified.

Validation of the classification tree: We tested the classification tree using external data (test data set),which have not contributed to the construction of the algorithm itself, and namely prescription data of 50 women, aged 18-45 years, who received a prescription of AEDs, but resident in a different area of the RER, the Ferrara Local Health Authority (358116 inhabitants in 2013). We used a three-step method:

First step: The Ferrara Health Trust supplied the prescription data concerning AEDs, antipsychotics and antidepressants, without disclosing whether the women belonged to the EPI or PSY cohort;

Second step: The hierarchical classification estimated using the training population was applied to the test population;

Third step : The cohorts were disclosed and the performance of the classification tree verified

3.3 Main study

3.3.1 Design

Retrospective observational population-based study.

3.3.2 Data sources and period of observation

Data were obtained from the following official regional registers:

Certificate of Delivery assistance (Certificato di Assistenza al Parto - CedAP): the certificate of delivery assistance registry was instituted in 2002 and records all deliveries in the regional territory including stillbirths and home childbirths. It is a nationwide registry. The following data are recorded: birth site, personal and socioeconomic information on parents, maternal obstetric history, pregnancy course, labour and delivery, neonate, malformations, stillbirths (http://salute.regione.emilia-romagna.it/siseps/sanita/cedap/files/Cedap_Rapporto_Nascita_2012.pdf);

Hospital Discharge Card (SDO): it contains the ICD codes of the discharge diagnosis;

Reimbursed drug prescription registries: SIT (Sistema Informativo Territoriale), AFT (Assistenza Farmaceutica Territoriale), DD (Distribuzione Diretta) and DPC (Distribuzione Per Conto) include all reimbursed prescriptions supplied to RER inhabitants. In particular, AFT records data from private pharmacies, while DD and DPC record drugs supplied by hospital pharmacies to outpatients. Each registry provides the following information: prescription date, unique code of drugs (that allows linkage with ATC and DDD archives), number of packages and units;

Emilia Romagna Registry of Congenital Malformations (IMER): the congenital malformation registry of the RER was instituted in 1978 in a few hospitals in the RER and since 1983 it has been a population-based program: yearly 40,000 births (coverage >95% of all births). Stillbirths at 26 weeks or more are included. Terminations of pregnancy have been collected since 1992. Reporting is made by a neonatologist and pediatricians during the first week of the infant's life. Selected malformations are followed up. Detailed exposure information is obtained by interviews of the mother of malformed infants (www.registroimer.it)

CedAP, SDO and drug prescription registries can be linked by a unique anonymous patient code.

IMER was linked to CEDAP using the following information: place of birth, child's date of birth, maternal date of birth, maternal residence. In case of multiple CeDAP cases linking to a single IMER case, the linkage was further refined using the following information: paternal date of birth, last menstruation period.

The period of observation was January 2009- December 2011.

3.3.3 Identification of pregnancies (deliveries and abortions)

We identified women inhabitants of RER who had had a delivery from the CEDAP and women inhabitants of RER who had had an abortion (induced or provoked) from the SDO (ICD codes related to abortions).

3.3.4 Drug exposure description

Active substances: The following AEDs (active substances) registered in Italy were considered: Phenobarbital (PB), Primidone (PRI), Phenytoin (PHT), Ethosuximide (ETS), Clonazepam (CNZ), Carbamazepine (CBZ), Oxcarbazepine (OXC), Rufinamide (RFN), Valproic acid (VPA), Vigabatrin (VGB), Tiagabine (TGB), Lamotrigine (LTG), Felbamate (FBM), Topiramate (TPM), Gabapentin (GBP), Levetiracetam (LEV), Zonisamide (ZNS), Pregabalin (PGB), Lacosamide (LCM).

Periods of observation:

Deliveries cohort: On the basis of the date of delivery and the gestational age at that time, 3 time periods were identified for each woman: the year preceding the delivery, the pregnancy period and the first trimester. For each period, exposure to AEDs was identified on the basis of prescriptions received, obtained by AFT, DD and DPC;

Abortions cohort: As the gestational age at the time of abortion is not traceable, we established to fix the trimester preceding the event as the AEDs exposure period in pregnancy;

Average daily dose: It was calculated as the ratio between the total amount of drug prescribed in the observation period and the number of days.

Stratification according to clinical indication

The exposed women were assigned to the EPI or the PSY group, according to the clinical indication drawn by the algorithm developed in the preliminary study. For this purpose we considered the prescribing data of the first six months of observation.

3.3.5 Identification and analysis of MCMs

Expert neonatologists reviewed every neonatal and foetal case detected through the IMER and separated cases of isolated MCM from cases with multiple congenital anomalies. Syndromic cases were included. Malformations were coded using a BPA (British Paediatric Association) modification of the WHOs ICD-9 (International Classification of Diseases, version 9) system (BPA, 1979).

3.3.6 Identification of stillbirths and foetal growth retardation

Stillbirths and cases of foetal growth retardation (FGR) were drawn from the CEDAP. FGR was defined as birthweight below the 10th percentile of the gender-specific birthweight for gestational age reference curves (WHO 1995).

3.3.7 Confounding factors

Maternal age, maternal education and smoking habit were drawn from the CEDAP. Reimbursable prescribed drugs belonging to FDA pregnancy categories X (contraindicated in pregnancy) or D (positive evidence of risk) were drawn from drug prescription registries. Maternal and foetal diseases that could affect the outcome were drawn from the SDO registry and drugs that could be considered proxy of maternal disease (ie: Insulin for diabetes) were drawn from the prescription registries.

3.3.8 Statistical analysis

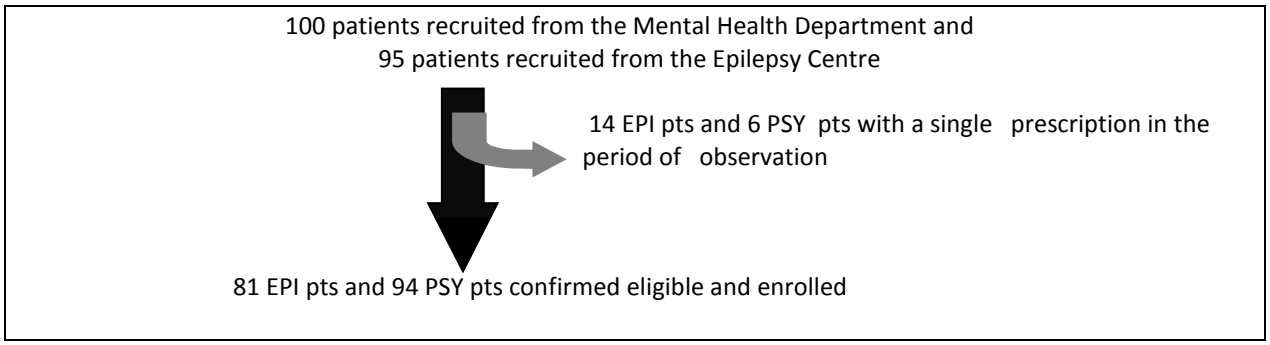
We estimated the rough Odds Ratios for abortion and MCM for AED exposure, using the variable as dichotomic and categorical (no AED, one AED, more AEDs). We also adjusted the Odds Ratios for MCMs for maternal confounding factors (age, education, smoking habit, diabetes, prescription of drugs belonging to X and D FDA pregnancy categories) and foetal confounding pathologies of different etiologies (i.e. cromosomopathy, infections, suspected radiation damage).

4. RESULTS

4.1 Identification of AEDs prescription patterns in women with and without epilepsy

Eighty-one subjects with epilepsy (EPI) and 94 with psychiatric diseases (PSY) were enrolled.

Figure 1- Flow chart of enrolled patients



AED monotherapy was the most common choice in both groups (69% EPI vs 79% PSY, p=0.15).

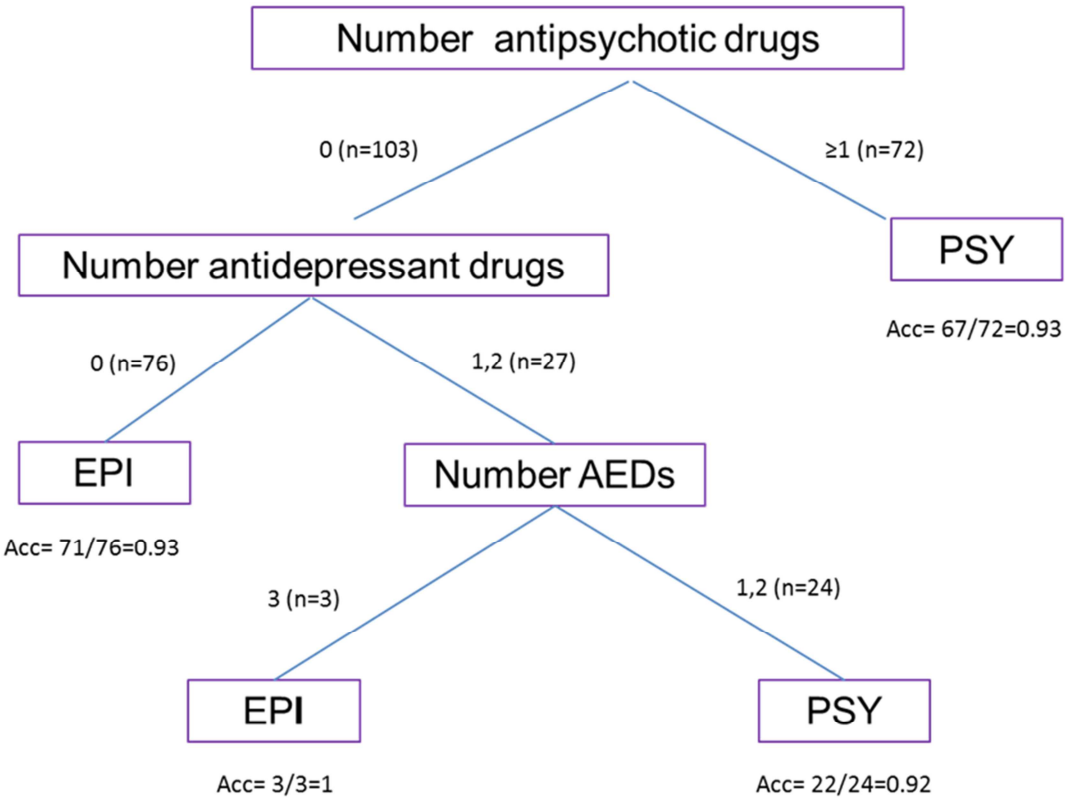
Phenobarbital, levetiracetam and zonisamide were used only in EPI, while pregabalin and gabapentin exclusively in PSY.

The intensity of treatment was higher in EPI than in PSY for clonazepam (0. 8 DDD vs 0.2), carbamazepine (0.7 vs 0.2), oxcarbazepine (>1 vs 0.2), valproate (>1 vs 0.4), lamotrigine (>1 vs 0.5), and topiramate (>1 vs 0.1).

Psychiatric co-treatments were less common in EPI than in PSY: antipsychotics were used in 6% vs 67% ($p<0.001$), lithium in none vs 9% ($p<0.001$) and antidepressants in 7% vs 70% ($p<0.001$).

The hierarchical classification system used prescriptions of antipsychotics, prescriptions of SSRIs and number of different AEDs to discriminate EPI and PSY with a probability greater than 0.93. Psychiatric co-therapies and therapy with ≥3FAE have the greatest discriminating power between EPI and PSI, as shown in Figure 2.

Figure 2 Hierarchical classification tree distinguishing EPI and PSY



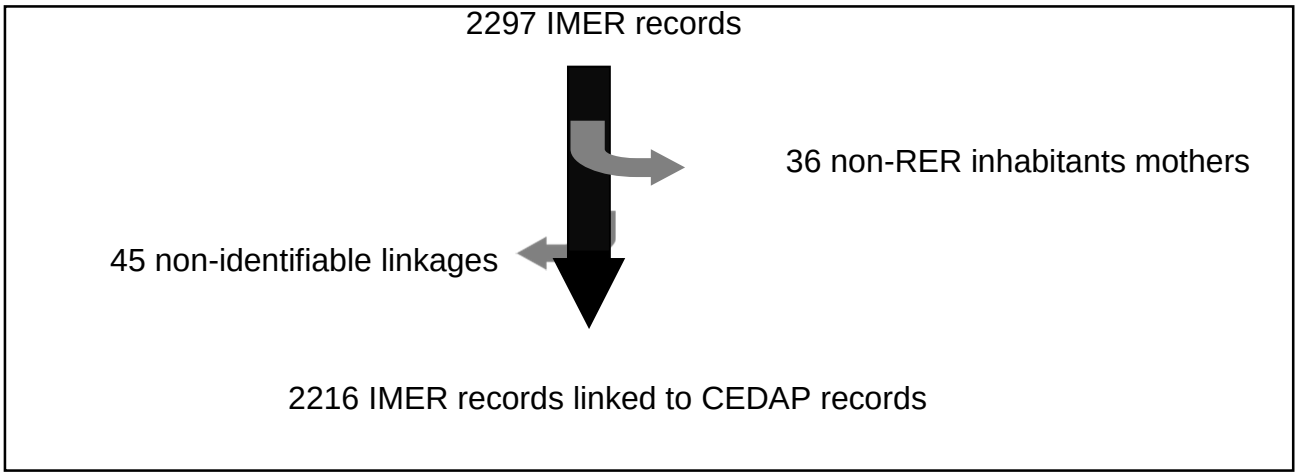
Acc= Accuracy (number of women correctly classified)
n= number of women in the node

The application of the algorithm to the 50 patients from Ferrara (44 with psychiatric disease, 6 with epilepsy) allowed a correct diagnosis in 45 patients (90%).

4.2 Linkage of IMER with other registries

The linkage of IMER with CeDAP generated 2216 univocally linked records, as shown in Figure 3.

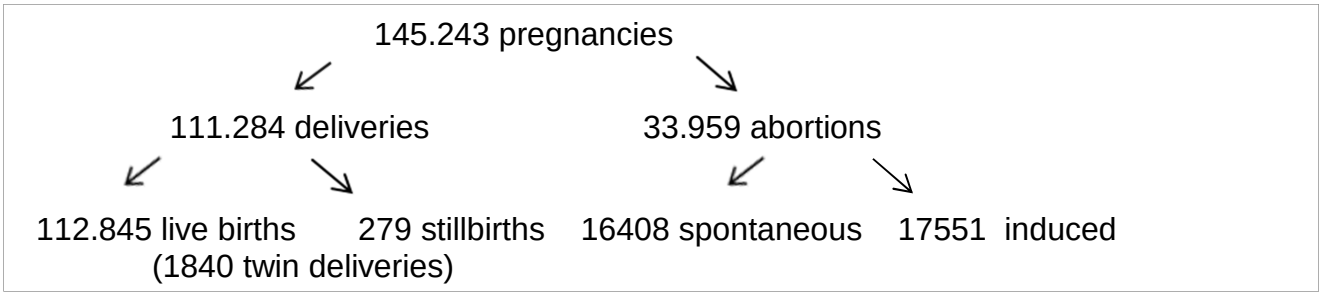
Figure 3- Flow chart of IMER-CEDAP linkage



4.3 Identification of pregnancies (deliveries and abortions) and drug exposure description

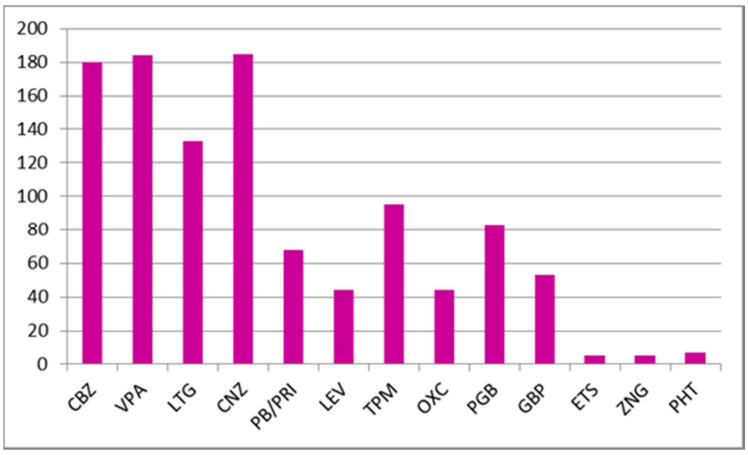
The cohort of pregnancies, comprising the cohort of deliveries and that of abortions is represented in figure 4.

Figure 4. Diagram of pregnancies, deliveries, abortions and newborns



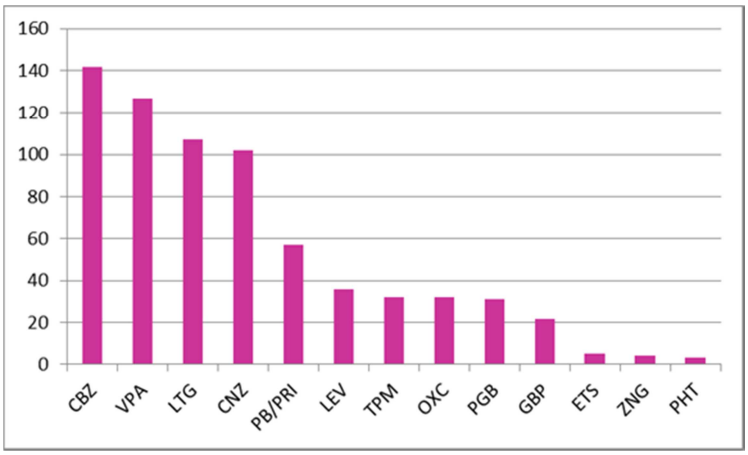
Nine hundred and forty-one women were exposed to AEDs during the year preceding the delivery/abortion (0.65%): 815 were exposed to one AED, 108 to 2 AEDs, 16 to 3 AEDs, 2 to 4 AEDs. The proportion of the single active substances is represented in figure 5. According to the algorithm, 561 of them (59,6%) had epilepsy.

Figure 5. AEDs exposure in the year preceding the delivery/abortion (n. of women)



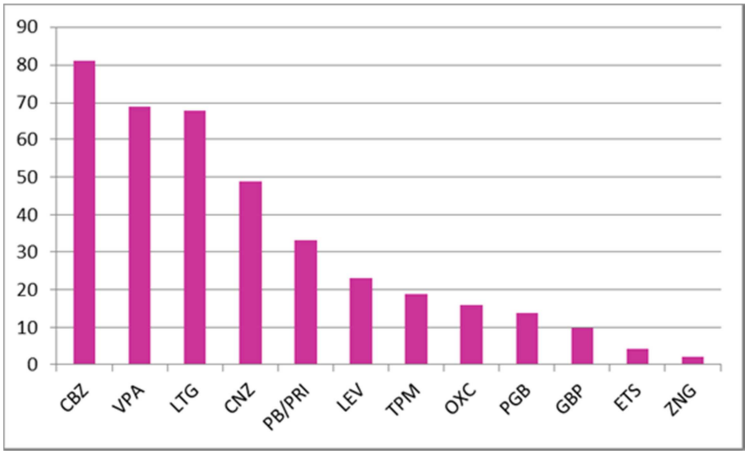
Six hundred and eleven women were exposed to AEDs during pregnancy (0.42%, 95% CI: 0.39-0.46%): 537 to one AED, 62 to two AEDs, 10 to 3 AEDs, 2 to 4 AEDs. The proportion of the single active substances is shown in Figure 6.

Figure 6. Exposure to AEDs during pregnancy (number of women)



Three hundred and fifty-three babies were exposed to AEDs during the first trimester of pregnancy (0.31%, 95% IC: 0.28-0.35%): 321 to one AED, 27 to two AEDs, 5 to three AEDs. The proportion of the single active substances is shown in Figure 7. According to the algorithm in 295 cases (83.6%) the maternal indication for AEDs was epilepsy.

Figure 7. Exposure to AEDs in the I trimester (number of newborns)



The average daily doses of the active substances are shown in Table 1. No woman in our population was exposed to Rufinamide, Tiagabine, Felbamate or Lacosamide.

Table 1 - Average daily dose for single active substance in the first trimester or in the trimester preceding the abortion

Active substance	Mean	St. dev	Median	1° quartile	3° quartile	N
Phenobarbital	97.2	43.4	94.4	66.7	133.3	44
Clonazepam	1.1	1.4	0.6	0.3	1.4	85
Carbamazepine	540.6	370.2	444.4	266.7	800.0	120
Oxcarbazepine	639.8	443.3	500.0	333.3	666.7	31
Valproate	508.8	385.4	366.7	200.0	666.7	116
Valpromide	800.0	565.7	800.0	400.0	1200	2
Lamotrigine	214.1	222.3	124.5	62.2	248.9	99
Topiramate	136.7	188.1	66.7	33.3	133.3	30
Levetiracetam	1556	1026	1333	1000	2000	33
Zonisamide	118.6	68.8	132.2	73.9	163.3	4

4.4 Exposure to AEDs and risk of abortion

Table 2 shows the outcome of the 145.243 pregnancies in the exposed and non-exposed women

Table 2-AEDs exposure and pregnancy outcome

Pregnancy outcome	Non-exposed		Exposed	
	N	%	N	%
Delivery	110871	76,7	413	67,6
Spontaneous abortion	16338	11,3	70	11,5
Induced abortion	17423	12,0	128	20,9
Total	**144632**	**100**	**611**	**100**

Table 3 and 4 show the risk of induced abortion (TOP: termination of pregnancy) and exposure to AEDs in the year preceding the event and in the trimester preceding the event (pregnancy). The risk of induced abortion was significantly increased after exposure to AEDs, with a positive relation to the number of taken AEDs.

Active substance	Exposed	N	TOPs	%	OR	95%	CI
All	No	128045	17319	13.5	1	.	.
	Yes	790	232	29.4	**2.658**	2.279	3.101
PB	No	128778	17541	13.6	1	.	.
	Yes	57	10	17.5	1.350	0.682	2.671
PRI	No	128832	17550	13.6	1	.	.
	Yes	3	1	33.3	NA	NA	NA
PHT	No	128829	17546	13.6	1	.	.
	Yes	6	5	83.3	NA	NA	NA
ETS	No	128831	17551	13.6	1	.	.
	Yes	4	0	0	NA	NA	NA
CNZ	No	128686	17497	13.6	1	.	.
	Yes	149	54	36.2	3.612	2.586	5.047
CBZ	No	128675	17507	13.6	1	.	.
	Yes	160	44	27.5	2.409	1.702	3.409
OXC	No	128797	17535	13.6	1	.	.
	Yes	38	16	42.1	4.616	2.424	8.790
VPA	No	128678	17504	13.6	1	.	.
	Yes	157	47	29.9	2.714	1.928	3.820
Valpromide	No	128832	17551	13.6	1	.	.
	Yes	3	0	0	NA	NA	NA
VGB	No	128834	17551	13.6	1	.	.
	Yes	1	0	0	NA	NA	NA
LTG	No	128722	17529	13.6	1	.	.
	Yes	113	22	19.5	1.536	0.964	2.447
TPM	No	128765	17525	13.6	1	.	.
	Yes	70	26	37.1	3.751	2.309	6.093
GBP	No	128796	17538	13.6	1	.	.
	Yes	39	13	33.3	3.172	1.630	6.174
LEV	No	128795	17541	13.6	1	.	.
	Yes	40	10	25	2.114	1.033	4.326
ZNS	No	128833	17551	13.6	1	.	.
	Yes	2	0	0	NA	NA	NA
PGB	No	128770	17524	13.6	1	.	.
	Yes	65	27	41.5	4.511	2.754	7.390

Table 3. Risk of induced abortion and exposure to AEDS in the year preceding the event

Table 4. Risk of induced abortion and exposure to AEDS in the trimester preceding the event

Active substance	Exposed	N	TOPs	%	OR	95%	CI
All	No	128294	17423	13.6	1	.	.
	Yes	541	128	23.7	**1.972**	1.616	2.406
PB	No	128788	17544	13.6	1	.	.
	Yes	47	7	14.9	1.114	0.500	2.485
PRI	No	128832	17550	13.6	1	.	.
	Yes	3	1	33.3	NA	NA	NA
PHT	No	128833	17549	13.6	1	.	.
	Yes	2	2	100	N.D	N.D	N.D
ETS	No	128831	17551	13.6	1	.	.
	Yes	4	0	0	NA	NA	NA
CNZ	No	128742	17524	13.6	1	.	.
	Yes	93	27	29	2.597	1.659	4.064
CBZ	No	128706	17524	13.6	1	.	.
	Yes	129	27	20.9	1.684	1.102	2.574
OXC	No	128806	17539	13.6	1	.	.
	Yes	29	12	41.4	4.479	2.139	9.379
VPA	No	128728	17521	13.6	1	.	.
	Yes	107	30	28	2.473	1.621	3.772
Valpromide	No	128833	17551	13.6	1	.	.
	Yes	2	0	0	NA	NA	NA
LTG	No	128744	17536	13.6	1	.	.
	Yes	91	15	16.5	1.252	0.719	2.178
TPM	No	128808	17545	13.6	1	.	.
	Yes	27	6	22.2	1.821	0.736	4.506
GBP	No	128815	17543	13.6	1	.	.
	Yes	20	8	40	4.229	1.728	10.346
LEV	No	128801	17543	13.6	1	.	.
	Yes	34	8	23.5	1.965	0.891	4.335
ZNS	No	128833	17551	13.6	1	.	.
	Yes	2	0	0	NA	NA	NA
PGB	No	128811	17544	13.6	1	.	.
	Yes	24	7	29.2	2.612	1.083	6.299

Table 5. Risk of induced abortion per number of AEDs

Exposure period	Number of AEDs	N	TOPs	%	OR	95%	CI
Previous 12 months	0	128045	17319	13.5	1	.	.
	1	687	196	28.5	**2.552**	2.161	3.014
	>=2	103	36	35	**3.435**	2.291	5.152
Pregnancy	0	128294	17423	13.6	1	.	.
	1	479	110	23	**1.897**	1.532	2.349
	>=2	62	18	29	**2.603**	1.504	4.506

4.5 Exposure to AEDs during the first trimester and risk of MCMs

During the three-year period of observation 2302 cases of newborns with MCMs were reported to the IMER. Nine were exposed to AEDs in utero, of whom 8 during the first trimester. According to the algorithm 6 of the mothers had epilepsy.

The incidence of MCMs was 2.3% in the newborns from exposed mothers (first trimester) and 2.0% in the newborns from non-exposed mothers. According to the clinical indication drawn by the algorithm, the incidence of MCMs in babies born to WWE exposed to AEDs was 2.0%.

The risk of MCMs increased when the mother was exposed to more than one AED, as reported in table 6.

The risk of MCMs for each single AED is reported in Table 7, while Table 8 reports the risk of MCMs for each AED in monotherapy or polytherapy.

The specific MCMs reported in the exposed group are listed in Table 9. The only anomaly which occurred in more than one baby was the ventricular septal defect (VSD). This MCM had a prevalence of 84.98 per 10000 liveborns in the exposed population versus 33.81 per 10000 liveborns in the not exposed. Table 9 reports also the supposed diagnosis according to the algorithm.

Table 6- AEDs number and MCMs

				Unadjusted			Adjusted*		
N of AEDs	N	MCMs	%	OR	95%	CI	OR	95%	CI
0	112771	2294	2	1	.	.	1	.	.
1	321	7	2.2	1.074	0.507	2.273	1.002	0.473	2.124
>=2	32	1	3.1	1.562	0.214	11.389	1.440	0.196	10.588

OR adjusted for maternal age, education, smoking habit, diabetes and prescription of drugs belonging to X and D FDA pregnancy categories and foetal confounding pathologies of different etiologies

Table 7- Single AEDs and risk of MCMs

					Unadjusted			Adjusted*		
Active substance	**Exposed**	**N**	**MCM**	**%**	**OR**	**95%**	**CI**	**OR**	**95%**	**CI**
All	No	112771	2294	2	1	.	.	1	.	.
	Yes	353	8	2.3	**1.117**	0.553	2.254	**1.042**	0.515	2.104
PB	No	113092	2301	2	1	.	.	1	.	.
	Yes	32	1	3.1	1.561	0.214	11.386	1.538	0.209	11.305
PRI	No	113123	2302	2	1	.	.	1	.	.
	Yes	1	0	0	N.D	N.D	N.D	N.D	N.D	N.D
ETS	No	113120	2301	2	1	.	.	1	.	.
	Yes	4	1	25	N.D	N.D	N.D	N.D	N.D	N.D
CNZ	No	113075	2301	2	1	.	.	1	.	.
	Yes	49	1	2	1.000	0.138	7.268	0.873	0.120	6.338
CBZ	No	113043	2300	2	1	.	.	1	.	.
	Yes	81	2	2.5	1.219	0.300	4.963	1.178	0.289	4.798
OXC	No	113108	2302	2	1	.	.	1	.	.
	Yes	16	0	0	N.D	N.D	N.D	N.D	N.D	N.D
VPA	No	113055	2302	2	1	.	.	1	.	.
	Yes	69	0	0	N.D	N.D	N.D	N.D	N.D	N.D
Valpromide	No	113122	2302	2	1	.	.	1	.	.
	Yes	2	0	0	N.D	N.D	N.D	N.D	N.D	N.D
LTG	No	113056	2301	2	1	.	.	1	.	.
	Yes	68	1	1.5	0.719	0.100	5.177	0.682	0.095	4.921
TPM	No	113105	2302	2	1	.	.	1	.	.
	Yes	19	0	0	N.D	N.D	N.D	N.D	N.D	N.D
GBP	No	113114	2300	2	1	.	.	1	.	.
	Yes	10	2	20	12.109	2.576	56.914	9.863	2.081	46.753
LEV	No	113101	2302	2	1	.	.	1	.	.
	Yes	23	0	0	N.D	N.D	N.D	N.D	N.D	N.D
ZNS	No	113122	2302	2	1	.	.	1	.	.
	Yes	2	0	0	N.D	N.D	N.D	N.D	N.D	N.D
PGB	No	113110	2301	2	1	.	.	1	.	.
	Yes	14	1	7.1	3.717	0.488	28.342	2.989	0.390	22.920

Table 8- Single AEDs and risk of MCMs in monotherapy/polytherapy

Active substance	Exposure	N	MCMs	%	OR	95%	CI
PB	No	113092	2301	2	-	-	-
	Monotherapy	23	0	0	-	-	-
	Politherapy	9	1	11.1	-	-	-
PRI	No	113123	2302	2	-	-	-
	Monotherapy	1	0	0	-	-	-
	Polytherapy	.	.	.	-	-	-
ETS	No	113120	2301	2	-	-	-
	Monotherapy	.	.	.	-	-	-
	Polytherapy	4	1	25	-	-	-
CNZ	No	113075	2301	2	1	-	-
	Monotherapy	44	1	2.3	1.120	0.154	8.134
	Polytherapy	5	0	0	N.D	N.D	N.D
CBZ	No	113043	2300	2	1	.	.
	Monotherapy	71	2	2.8	1.396	0.342	5.696
	Polytherapy	10	0	0	N.D	N.D	N.D
OXC	No	113108	2302	2	-	-	-
	Monotherapy	14	0	0	-	-	-
	Polytherapy	2	0	0	-	-	-
VPA	No	113055	2302	2	-	-	-
	Monotherapy	59	0	0	-	-	-
	Polytherapy	10	0	0	-	-	-
Valpromide	No	113122	2302	2	-	-	-
	Monotherapy	1	0	0	-	-	-
	Polytherapy	1	0	0	-	-	-
LTG	No	113056	2301	2	1	.	.
	Monotherapy	59	1	1.7	0.830	0.115	5.994
	Polytherapy	9	0	0	N.D	N.D	N.D
TPM	No	113105	2302	2	-	-	-
	Monotherapy	15	0	0	-	-	-
	Polytherapy	4	0	0	-	-	-
GBP	No	113114	2300	2	-	-	-
	Monotherapy	6	2	33.3	24.090	4.410	131.588
	Polytherapy	4	0	0	N.D	N.D	N.D
LEV	No	113101	2302	2	-	-	-
	Monotherapy	14	0	0	-	-	-
	Polytherapy	9	0	0	-	-	-
ZNG	No	113122	2302	2	-	-	-
	Monotherapy	2	0	0	-	-	-
	Polytherapy	.	.	.	-	-	-
PGB	No	113110	2301	2	1	.	.
	Monotherapy	12	1	8.3	4.378	0.565	33.923
	Polytherapy	2	0	0	N.D	N.D	N.D

Table 9- Types of MCMs in children from exposed mothers

Type of MCM	Number of affected babies	AEDs	Supposed diagnosis
Ventricular septal defect(VSD)	3	GBP; GBP; PGB	Epi; Epi; Psy
Atrial septal defect, tricuspid insufficiency	1	LTG	Epi
Bilateral Postaxial polydactyly	1	CBZ	Epi
Ectopic Kidney	1	CNZ	Psy
Congenital diaphragmatic hernia	1	CBZ	Epi
Multiple congenital Anomalies + Hypospadias	1	PB+ETS	Epi

4.6 Exposure to AEDs and risk of stillbirth

During the period of observation there were 278 stillbirths in the non-exposed group, with an incidence of 25 per 10.000 and 1 in the exposed group, with an incidence of 28 per 10.000

4.7 Exposure to AEDs and risk of fetal growth retardation (FGR)

Table 10 reports the risk of FGR per number of AEDs and table 11 and 12 report the risk of FGR for single AEDs use in pregnancy and in the first trimester. There is a slightly higher risk for FGR after exposure to AEDs in the first trimester, increasing with polytherapy.

Table 10- Risk of foetal growth retardation per number of AEDs

Exposure period	Number of AEDs	N	FGR	%	OR	95%	CI
Previous 12 months	0	112562	11201	10	1	.	.
	1	495	57	11.5	1.177	0.893	1.553
	>=2	67	10	14.9	1.592	0.813	3.116
Pregnancy	0	112708	11215	10	1	.	.
	1	372	48	12.9	1.341	0.990	1.817
	>=2	44	5	11.4	1.160	0.457	2.944
First trimester	0	112771	11220	9.9	1	.	.
	1	321	43	13.4	1.401	1.015	1.932
	>=2	32	5	15.6	1.683	0.649	4.365

Table 11- Fetal growth retardation and AEDs use during pregnancy

Active substance	Exposure	N	FGR	%	OR	95%	CI
All	No	112708	11215	10	1	.	.
	Yes	416	53	12.7	**1.322**	0.990	1.764
PB	No	113084	11263	10	1	.	.
	Yes	40	5	12.5	1.292	0.506	3.297
PRI	No	113122	11268	10	1	.	.
	Yes	2	0	0	N.D	N.D	N.D
PHT	No	113124	11268	10	1	.	.
ETS	No	113120	11268	10	1	.	.
	Yes	4	0	0	N.D	N.D	N.D
CNZ	No	113057	11257	10	1	.	.
	Yes	67	11	16.4	1.776	0.930	3.391
CBZ	No	113021	11260	10	1	.	.
	Yes	103	8	7.8	0.761	0.370	1.566
OXC	No	113107	11267	10	1	.	.
	Yes	17	1	5.9	0.568	0.076	4.262
VPA	No	113046	11257	10	1	.	.
	Yes	78	11	14.1	1.487	0.786	2.812
Valpromide	No	113122	11267	10	1	.	.
	Yes	2	1	50	N.D	N.D	N.D
VGB	No	113124	11268	10	1	.	.
LTG	No	113048	11259	10	1	.	.
	Yes	76	9	11.8	1.214	0.605	2.436
TPM	No	113103	11266	10	1	.	.
	Yes	21	2	9.5	0.952	0.222	4.086
FBM	No	113112	11263	10	1	.	.
	Yes	12	5	41.7	6.460	2.050	20.356
LEV	No	113098	11265	10	1	.	.
	Yes	26	3	11.5	1.192	0.360	3.951
ZNS	No	113122	11267	10	1	.	.
	Yes	2	1	50	N.D	N.D	N.D
PGB	No	113107	11265	10	1	.	.
	Yes	17	3	17.6	1.959	0.565	6.786

Table 12- Fetal growth retardation and AEDs use during the first trimester

Active substance	Exposure	N	FGR	%	OR	95%	CI
All	No	112771	11220	9.9	1	.	.
	Yes	353	48	13.6	**1.426**	1.051	1.934
PB	No	113092	11263	10	1	.	.
	Sì	32	5	15.6	1.681	0.648	4.360
PRI	No	113123	11268	10	1	.	.
	Sì	1	0	0	N.D	N.D	N.D
PHT	No	113124	11268	10	1	.	.
ETS	No	113120	11268	10	1	.	.
	Sì	4	0	0	N.D	N.D	N.D
CNZ	No	113075	11260	10	1	.	.
	Sì	49	8	16.3	1.775	0.833	3.781
CBZ	No	113043	11262	10	1	.	.
	Sì	81	6	7.4	0.723	0.315	1.661
OXC	No	113108	11267	10	1	.	.
	Sì	16	1	6.3	0.605	0.080	4.563
VPA	No	113055	11257	10	1	.	.
	Sì	69	11	15.9	1.724	0.906	3.281
Valpromide	No	113122	11267	10	1	.	.
	Sì	2	1	50	N.D	N.D	N.D
VGB	No	113124	11268	10	1	.	.
LTG	No	113056	11259	10	1	.	.
	Sì	68	9	13.2	1.380	0.684	2.783
TPM	No	113105	11266	10	1	.	.
	Sì	19	2	10.5	1.065	0.246	4.606
GBP	No	113114	11264	10	1	.	.
	Sì	10	4	40	6.027	1.701	21.361
LEV	No	113101	11265	10	1	.	.
	Sì	23	3	13	1.356	0.403	4.564
ZNS	No	113122	11267	10	1	.	.
	Sì	2	1	50	N.D	N.D	N.D
PGB	No	113110	11265	10	1	.	.
	Sì	14	3	21.4	2.466	0.688	8.839

5. DISCUSSION

A first achievement of our study was the design of an algorithm which proved to be very accurate in discriminating women who are AEDs users for epilepsy from women who use them for a psychiatric disorder, on the basis of their prescriptions. The application of the algorithm to external data resulted in a good predictive ability of the diagnosis based on the prescription pattern showing, by comparison with the actual diagnosis, an error rate of 10% (5 subjects out of 50), dramatically close to the cross validation estimate. An obvious limitation of this approach is that it cannot be applied to other clinical indications. Women who use AEDs for other disorders, such as migraine, would probably be misclassified as epileptic, as they generally do not have psychiatric co-prescriptions. For our purpose, we hypothesized that the algorithm could prove useful, as, in pregnant women, indications different from epilepsy and psychiatric disorders are supposed to be very rare.

The prevalence of AEDs use in the first trimester of pregnancy in our population, 4 per 1000 pregnancies, or 3.1 per 1000 deliveries, is comparable to the data reported by other Authors (Czeizel et al., 1992; Malm et al., 2003; Wide et al., 2004; Kilic et al., 2014; Wen et al., 2015). Our results could be slightly underestimated, as clobazam, a benzodiazepine not rarely used in epilepsy, is not reimbursable and therefore not traceable. However, this drug is only very rarely used as a monotherapy, so it is unlikely that a significant proportion of exposed women were misclassified as unexposed.

Unlike recent reports from Denmark and the USA (Kilic et al., 2014; Wen et al., 2015), according to which lamotrigine was the most used drug in pregnancy, carbamazepine was the most used AED in RER, being taken in 23% of all the exposed pregnancies. Levetiracetam was much less used in our population (5.9% of the total used AEDs) than it was described in the more recent literature (Meador et al., 2009; Moolgard-Nielsen and Hviid, 2011; Kilic et al., 2014; Wen et al., 2015). It is likely that prescribing patterns vary in different regions. A striking finding of our study is that approximately one in five AEDs users was taking valproate, which is currently known as the most dangerous AED in pregnancy, due to its higher teratogenic risk, but also to possible cognitive and developmental detrimental effects as demonstrated by recent studies (Velez-Ruiz NJ and Meador KJ, 2015). One possible explanation of the unexpected over-representation of valproate is that this drug is used both in epilepsy and in psychiatric disorders; indeed one study investigating trends of use of AEDs in pregnant women showed that over time valproate use decreased overall, but not in patients with a psychiatric disorder (Wen et al., 2015). It is worth considering also that valproate is still one of the most effective drugs in some type of seizures and epileptic syndromes, and in particular generalized idiopathic epilepsies, which are common in the young (Marson et al., 2006) and it showed to be more effective in maintaining seizure freedom in pregnancy than less teratogenic drugs (EURAP Study Group, 2006; Hernandez-Diaz et al., 2012). Lastly, taking into account the limitations of the ascertainment methods, the mean dose of VPA in our population should be considered a low dose, associated with a lower risk (Tomson et al., 2011; Hernandez-Diaz et al., 2012; Campbell et al., 2014).

However, an auditing with the neurologists and psychiatrists of the Region could be beneficial for verifying and raising their awareness of the warnings on the use of valproate in women of childbearing age.

One very interesting finding of our study was the almost two-fold risk of induced abortion in women taking AEDs; furthermore there is a clear trend towards an increased risk when more than one AED is used. There is one first important limitation in case ascertainment of abortions: due to the Italian privacy policy, the ICD codes related to induced terminations of pregnancy are no longer reported in the Hospital discharge registry (SDO) with the unique anonymous code which allows to link these data to the other registers. However, since adjustments to the law have been carried out at different times, data from some hospitals were available for a longer period, including our period of observation. Overall, considering the regional anonymous statistical data (ISTAT) for the previous years (the ones concerning the period 2009-11 are not available yet) we estimated that approximately one half of the induced abortions were lost. We believe that this did not significantly affect our results. In fact there is no reason to hypothesize that in some hospitals women taking AEDs were more represented among women who underwent an abortion, than in others. A possible explanation for our results on abortions could be an excess of malformations in the exposed foetuses , detected by prenatal ultrasound. This would be relevant, indicating that studies on malformations detected only on deliveries are only partially reliable. On the other hand, physicians taking care of women with epilepsy well know from their everyday practice that a significant number of them, faced with an unplanned pregnancy, choose very early to terminate their pregnancy, due to a groundless fear of the pregnancy outcome. These "unnecessary" abortions are the result of a malpractice which would deserve, as well, to be clearly delineated and effectively tackled. Unfortunately, again due to the Italian privacy policy, it was impossible to have further information on the abortions, including the gestational age, which could have allowed the distinction between abortion in the first trimester, in which a malformation could very rarely have been identified, and abortions in the second trimester, in which a severe pathology of the foetus or, much more rarely, of the mother, must have been present. Further studies are needed to understand the excess of terminations of pregnancy in this population.

In agreement with the literature data, the rate of spontaneous abortions was almost superimposable in the exposed and non-exposed women and so was the risk of stillbirth.

The malformation rate in the exposed population exceeded only slightly the one of the non-exposed, indeed, after adjusting for confounding factors the OR was very close to 1 (1.042). However the risk increased on polytherapy, showing an evident trend to a higher risk after exposure to AEDs.

Caution is needed in speculating on single AEDs or specific malformations, due to the little number of MCMs. However we found a significant higher risk of ventricular septal defect, which had a more than twofold higher prevalence in the exposed population. Interestingly, in two of the three cases, there was a maternal exposure to gabapentin and in the third to pregabalin, a molecule which has a similar chemical and pharmacodynamic profile. In the literature there are still a few data on teratogenicity of gabapentin, which seem to point

toward a low risk. However, the only malformation reported over 11 exposures was ventricular septal defect in the study by Morrow et al. (2006) and the only malformation reported over 59 exposures was a not further specified “congenital heart disease” in the study by Molgaard-Nielsen and Hviid (2011). Further larger studies are needed to investigate a possible association between intrauterine exposure to gabapentin and pregabalin and ventricular septal defect.

According to our algorithm, 6 out of 8 women who gave birth to a child with a congenital anomaly, had epilepsy. This result would lead to an incidence of MCMs in babies born to WWE exposed to AEDs of 2.0%, equal to the one of the non-exposed population. However two of them were on monotherapy with gabapentin. As this drug is commonly used in monotherapy for neuropathic pain, and this diagnosis would not be ruled out by our algorithm, we believe more caution than previously thought must be used to interpret the result. Further refinements of the algorithm, allowing the inclusion of women with indications other from epilepsy and psychiatric disorders might be needed, as these indications might be more frequent in pregnancy than expected (Guttuso et al., 2014).

In agreement with some studies, we found that being exposed to AEDs in utero, and especially in the first trimester, carried a slightly higher risk of fetal growth retardation. The risk was higher in polytherapy.

CONCLUSIONS

The prevalence of AED use in pregnancy in Emilia Romagna Region is similar to the one found in other regions and countries, concerning approximately 4 out of 1000 pregnancies.

Valproate might be over-used in pregnancy in Emilia Romagna. An audit with neurologists and psychiatrists could be beneficial for raising awareness on the appropriateness of switching to another, less teratogenic drug, whenever possible.

Our data indicate that major congenital malformations and other foetal adverse outcomes do show a slightly higher prevalence after intrauterine exposure to AEDs, especially in polytherapy, but they are still infrequent. For this reason pregnancy should not routinely be designated at high risk in patients taking these drugs.

Further studies are needed to investigate a possible association between intrauterine exposure to gabapentin and pregabalin and ventricular septal defect.

To our knowledge, this is the first study investigating the prevalence of induced termination of pregnancy in women taking AEDs. Even taking into account the limitations of case ascertainment, the high prevalence of induced abortions in our population raises concerns and deserves further studies to clarify its causes.

This work allowed the creation of a network among neurologists, gynaecologists, neonatologists and pharmacologists and led to the design of a dedicated database that links data on AEDs prescriptions, deliveries, congenital anomalies and other foetal outcomes. Therefore it may constitute the premises for a permanent surveillance system of pregnancy outcomes in women taking AEDs in the Emilia Romagna Region.

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APPENDIX 1

Abbreviations used in the text

AED	**Antiepileptic Drugs**
GTCS	**Generalized tonic-clonic seizures**
MCM	**Major Congenital Malformation**
PB	**Phenobarbital**
PHT	**Phenytoin**
VPA	**Valproate**
CBZ	**Carbamazepine**
LTG	**Lamotrigine**
LEV	**Levetiracetam**
TPM	**Topiramate**
WWE	**Women With Epilepsy**
RER	**Regione Emilia Romagna**
ATC	**Anatomical Therapeutic Chemical (classification system)**
FGR	**Foetal Growth Retardation**

APPENDIX 2

AEDs indications other than epilepsy (including off-label indications)

Clonazepam (CNZ)	Anxiety, insomnia, restless legs syndrome, tremor, myoclonus
Carbamazepine (CBZ) and oxcarbazepine (OXC)	trigeminal neuralgia, bipolar syndrome, neuropathic pain, myotonia, cramps, alcohol withdrawal syndrome
Gabapentin (GBP), Pregabalin (PGB)	Neuropathic pain, trigeminal neuralgia, tremor, fibromyalgia
Lamotrigine (LTG)	migraine prophylaxis, SUNCT syndrome, neuropathic pain, fibromyalgia
Phenobarbital (PB) and primidone (PRI)	Anxiety, other barbiturates withdrawal syndrome, essential tremor
Topiramate (TPM)	migraine prophylaxis, alcoholism, obesity
Valproic acid (VPA)	migraine prophylaxis, bipolar syndrome

ACKNOWLEDGEMENTS

First and foremost I would like to thank Prof. Paolo Tinuper for having given me the opportunity to conduct this absorbing study and for having taught me most of what I know on epilepsy.

I would like to thank all the people who worked on this project and in particular all the ESPEA (Emilia Romagna Study on Pregnancy Exposure to Antiepileptic drugs) Group members: Gabriele Accetta, Gianni Astolfi, Sergio Battaglia , Francesca Bisulli, Guido Cocchi, Letizia Conti, Alessandra Curti , Roberto D'Alessandro, Camilla Lupi, Ilaria Naldi, Carlo Piccinni, Elisabetta Poluzzi, Nicola Rizzo, Giuliana Simonazzi, Paolo Tinuper.

I thank Cecilia Baroncini for editing the English text.

This project was funded by the Italian Ministry of Health-Research Program RF 2010-2315893.