Risk assessment of antiepileptic drugs in pregnancy

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ISBN: 978 94 6070 44 6
Cover design & typesetting: Nynke Tiekstra, ColtsfootMedia, Noordwolde
Printed by: idDruk, Hoogenveen

Paranimfen: Marlies Vogel-Schippers
Cornelis Boersma

RIJKSUNIVERSITEIT GRONINGEN

RISK ASSESSMENT OF ANTIEPILEPTIC DRUG USE IN PREGNANCY

Proefschrift

ter verkrijging van het doctoraat in de
Wiskunde en Natuurwetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus, dr. E. Sterken,
in het openbaar te verdedigen op
vrijdag 9 december 2011
om 14:30 uur

door

Janneke Boersma-Jentink
geboren op 30 november 1983
te Balkbrug, gemeente Avereest

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GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

Background

Pregnancy results in a lot of changes in the female body. Therefore pregnancy can influence the disease status of the woman as well as the pharmacodynamics and –kinetics of drugs [1-2]. As pregnant women are generally excluded from clinical trials for ethical reasons, hardly any drug information is available on efficacy and safety prior to market approval [3-4]. This lack of experience makes pregnant women (and their unborn child) a very vulnerable group of patients.

Due to lack of efficacy and safety evidence, and the fear for teratogenicity, doctors often rely on their own experience and it is therefore likely that they prescribe to pregnant women older rather than newer drugs [5-6]. These older drugs, like for example methyldopa for hypertension, are no longer prescribed as a first or second choice drug for non-pregnant women, as newer treatment options are more effective or are associated with less adverse effects [7].

A teratogen is an agent causing malformations during the prenatal development. The human embryo is most susceptible for teratogenicity from 3 to 12 weeks after conception [2]. In a broader sense teratogenicity can be defined as developmental toxicity and includes: altered growth (including growth retardation), functional deficits or impairments, malformations and death [2]. This thesis will focus on physical major congenital malformations. In particular, this means that the chapters do not consider the risk of behavioural development, such as mental retardation.

To keep track on the teratogenicity and other adverse effects of drugs used by pregnant women, observation and recording of daily practice drug use is very important. Collecting evidence in daily practice is a time-consuming task and it requires long follow-up to confirm or rule out potential teratogenicity [8]. This is nicely described in a paper of Lo and Friedman stating that no adequate information is available for pregnant women and their health care professionals for most drugs that were approved to the market the last 20 years [4].

However, to obtain more information on effectiveness and safety of maternal drug use, proper registration is highly important [9]. Both the prospective registration of exposure to these drugs and later on their pregnancy outcome, in specific 'Disease & Drug *Registries*' (e.g. epilepsy and antiepileptic drug registries) and registration of negative outcomes in 'R*egistries of Malformations*' (e.g. EUROCAT network of congenital malformations or Slone Epidemiology Center) are valuable. Especially because the restrictive

factor in studies looking at specific malformations associated with specific drugs, is the number of (exposed) pregnancy outcomes included [10-12]. This power problem is nicely put into words by Michale Papagiannis: 'The absence of evidence is not the evidence of absence'.

It is important to investigate the risk for general malformations to get an idea of the overall teratogenicity of a drug. However, as most drugs, with an increased risk for teratogenicity, are associated with a specific malformation or a small range of malformations, this specific increase is often not seen in a significant increased rate for overall malformation [8]. For example a drug is associated with a four times increased risk for orofacial clefts (prevalence 1 per 1000). The total prevalence of any malformation will increase from 3% to 3.3%, which is (still 3% and) within the normal variation.

In the trajectory of gathering information about the safety of drug use in pregnancy, several study designs are important [13]. Descriptive studies – like case reports and case series – are informative in the period direct after market approval when hardly any information is available. Later on, small cohort studies can provide information on the risk for malformations in general and moreover these cohort studies can provide indications for possible associations with specific malformations. These indications can best be tested in a population-based case-control designed study. This specific design allows for calculation of a more powered estimate of the risk for associations found. Unfortunately, most population-based datasets that are appropriate for case-control studies do not include a random sample of non-malformed controls. Therefore, either external groups or malformed control groups are used. External control groups are used as a proxy for drug exposure in the general pregnant population. For malformed controls, the results are presented relative to other malformed outcomes and not compared to the general pregnant population. In case of malformed controls, it is assumed that no relation exists between the malformations included in the control group and the exposure under study or the malformations investigated. By using a wide range of malformations assumed to be unrelated to the exposure, the effect of one potential relation is small. Among such a control group, consisting of pregnancy outcomes not associated with the drug under study, the exposure to the drug under study is assumed to be representative for the use of this drug in the general pregnant population.

Major disadvantages of the use of observational data compared to data from randomized clinical trials are the occurrence of bias and confounding [8, 13-14]. In clinical trials drugs are randomly assigned to the patient which means that there is implicitly controlled for all possible influencing factors

(if possible, depending on sample size). However, in daily practice there are often differences between patients with the same disease who are receiving different drugs or diagnostic tests (selection bias). And records reporting maternal drug exposure of patients might be more complete for pregnancies with a malformed pregnancy outcome compared to those with a non-malformed outcome (information bias). In case of chronic diseases and increased risks for teratogenicity there always is an additional problem: is the disease or the drug associated with the teratogenic event? In case of epilepsy and antiepileptic drugs this confounding by indication issue is also relevant. The disease might increases the risk for the foetus, although the risk induced by the drug is higher in a woman with good disease control [15-16].

This thesis will focus on the use of antiepileptic drugs around pregnancy. The use of antiepileptic drugs is defined as the use of any drug having an ATC-code starting with 'N03A', irrespective of prescribed indication [17]. The name 'antiepileptic drug' assumes use for the indication of epilepsy. However, the approved indications of some drugs classified as antiepileptic drug are much wider: anxiety disorders, central or peripheral neuropathic pain, depressive or manic episodes in bipolar disorders, essential tremor, infantile spasms and migraine [18].

Compared to the indication of epilepsy, treatment decisions involving switching or stopping the antiepileptic drug might be easier for some of these other indications in case of a child wish, such as for migraine [19]. Still, if the drug use is continued during the first trimester of pregnancy the teratogenic risk will be the same irrespective of the indication, at least if the dosage used is comparable.

To individually assess the treatment options for women requiring antiepileptic drugs, it is important that they visit their health care professional to discuss possible suitable alternatives and to make treatment decisions early, before pregnancy. In case of antiepileptic drugs, most women will need to continue using them if they get a child wish. Therefore, it is highly important to investigate and compare the risks of the treatment options for these women.

Within the field of teratology these investigations and comparisons are mainly pure epidemiological. However, also economic evaluations are considered to be of increasing importance for drug assessments. In particular, the drug that is chosen to be used/continued during pregnancy could be interpreted as a safety intervention for the offspring. Which may result in high cost-effectiveness ratio's being accepted [20].

Additional to treatment decisions being discussed before getting pregnant, it is important for all women with a child wish to start using folic acid [21]. Although direct evidence is lacking folic acid use is thought to be

more important for women using antiepileptic drugs (compared to the general pregnant population). In particular, in the summary of product characteristics of valproic acid 5 mg folic acid is recommended for women using valproic acid [22].

The goal of this thesis is to investigate the use of antiepileptic drugs around pregnancy, to provide a risk assessment related to teratogenicity of the most frequently used antiepileptic drugs, to show the impact of these teratogenic risks in daily practice and to provide a health economic view on teratogenicity. The risk assessment studies included in this thesis are the first combining international EUROCAT data to assess the risk of a specific drug on specific malformations.

For the studies presented in this thesis two datasets were used: the international EUROCAT network of congenital malformations and the IADB.nl including pharmacy prescription data [23-27]. These datasets have some important characteristics in common. Both databases are population-based continuing surveillance systems in which data is entered locally and kept centrally. More information about the IADB.nl and the EUROCAT network can be found in box I and II.

Box I

The IADB.nl is a longitudinal, population-based pharmacy prescription database in the Netherlands established in 1999. Data is collected form 55 pharmacies covering about half a million people. Case data starts in 1994. The IADB.nl includes all prescriptions of community pharmacies. Prescriptions during hospitalization and information about OTC drugs are not available. Within the IADB.nl, a pregnancy database is set up by linkage of the address code of a child with a woman aged 15-50 at birth of the child with the same address code. Approximately 65% of all children can be linked to one potential mother and are available in the pregnancy database. As only the date of birth is known and not the actual gestational length, the length of each pregnancy is estimated 273 day (divided into three trimesters of 91 days). The use of the pregnancy database is especially suitable for drugs used for chronic indications like antiepileptic drugs in which the exact timing in less important as the exposure is constant. Studies presented in chapter 1 and 2 contain data derived from the IADB.nl

Box II

EUROCAT network
EUROCAT (European Surveillance of Congenital Anomalies) is a population-based network of local congenital malformation registries established in 1979. The network grew in time and currently the network consists of 42 registries covering over 1.7 million births per year (>30% of all births in the European Union). Information is recorded of all livebirths, stillbirths (gestational age ≥20 weeks) and terminations of pregnancy following prenatal diagnosis, affected with major structural malformations, chromosomal anomalies, syndromes or other hereditary conditions associated with structural malformations. Isolated minor malformations are not collected centrally (EUROCAT guide 3.2). Up to eight malformations and one syndrome per case are coded locally using ICD9 or in more recent years ICD10 codes with extension codes from the British Pediatric Association. Additionally to variables concerning the diagnosis of malformations variables providing information about 'baby and mother', exposure, family history and socio-demographic are available, but not all obligatory. Local registries have their own policy and methods to collect the data and multiple sources are used. Once or twice a year data are transmitted to the Central registry.

Antiepileptic Study Database and EUROmediCAT
Within EUROCAT several Working Groups exist. One of them, the Medication during pregnancy working group, aims to develop and implement post marketing surveillance of teratogenic risks of medications (used for maternal chronic diseases). To achieve this, a reproductive pharmacovigilance case-control monitoring system will be developed: EUROmediCAT. One of the milestones was the creation of the EUROCAT Antiepileptic Study Database in 2007. All local registries with good maternal drug exposure data were invited to participate in this dataset. The exact criteria were: 1) maternal antiepileptic drug use or epilepsy reported for at least 3 per 1000 registrations, and 2) specific drug name or complete ATC code available for at least 80% of the antiepileptic drug exposed pregnancies. At the start of the project 19 local registries met these inclusion criteria and were willing to participate. The studies performed with this database are presented in chapter 3, 4 and 5 of this thesis.
The development of the pharmacovigilance case-control monitoring system continues with the start of an EU Framework 7 funding March 2011. Some of the goals of this project are to enhance the maternal exposure data by linkage with existing datasets containing drug prescription data, and to provide risk assessment of drug exposure in the first trimester of pregnancy associated with teratogenicity.

Outline thesis

In this thesis, epidemiological and health economic aspects of antiepileptic drug use around pregnancy are described and evaluated. The thesis consists of three parts.

In *part I* of this thesis entitled '*Drug utilization patterns in the general pregnant population*', two drug utilization studies are presented to determine the use of drugs around pregnancy in the general pregnant population. *Chapter 1* describes the use of drugs from two years before pregnancy until three months after delivery in the Netherlands, based on the IADB.nl a community pharmacy prescription database. In *chapter 2* the use of antiepileptic drugs around pregnancy is described for three European countries: France, Italy and the Netherlands.

Part II entitled *'Risk assessment of antiepileptic drugs in the first trimester of pregnancy'* three international, multi-centre, population-based case-control studies are performed. In *chapter 3* the indication of the association between lamotrigine exposure in the first trimester of pregnancy and the risk for orofacial clefts is tested. Next in *chapter 4* and *chapter 5* two systematic literature reviews are performed to find indications of specific major congenital malformations associated with respectively valproic acid and carbamazepine. The indications identified in the literature are tested in a case-control study using malformed controls.

The last part of the thesis, *part III* entitled *'Considerations for treatment practice'* consists of another case-control study and an economic evaluation. C*hapter 6* describes a case-control study estimating the protective effect of folic acid on the risk for spina bifida in women using valproic acid. Whether or not folic acid helps to protect against the type of spina bifida caused by valproic acid is uncertain. Finally, the economic consequences of the choice for a specific antiepileptic drug in young women with childbearing potential are described in *chapter 7,* applying the societal perspective.

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Part I

Drug utilization patterns in the general pregnant population

1 DRUG PRESCRIPTION PATTERNS BEFORE, DURING AND AFTER PREGNANCY FOR CHRONIC, OCCASIONAL AND PREGNANCY-RELATED DRUGS IN THE NETHERLANDS

MK Bakker, J Jentink, F Vroom, PB Van Den Berg, HEK De Walle, LTW De Jong-Van Den Berg

BJOG 2006;113:559-568

Objective: To compare the prescription of drugs in women over a period from 2 years before until 3 months after pregnancy, regarding the type of drugs used and the fetal risk.

Design and Setting: A cohort study based on pharmacy records of women giving birth to a child between 1994 and 2003. The study was performed with data from the InterAction database, containing prescription-drug-dispensing data from community pharmacies.

Population: The study population included 5412 women for whom complete pharmacy records were available.

Methods and outcome measures: Drugs were classified into three categories: (1) drugs for chronic conditions, (2) drugs for occasional use and (3) drugs for pregnancy-related symptoms and also classified according to the Australian classification system. The prescription rate was calculated as the number of women per 100 women who received one or more prescriptions for a given drug within a specified time period.

Results: About 79.1% of the women received at least one prescription during pregnancy. The prescription rate for most drugs for chronic diseases and for occasional use decreased during pregnancy, whereas, as expected, the prescription rate for pregnancy-related drugs increased. During the first trimester of pregnancy, 1.7% of all drugs prescribed for chronic conditions and 2.3% of the occasional drugs were classified as harmful.

Conclusions: The increase in prescription rate during pregnancy is caused by an increase in prescription rate of drugs for pregnancy-related symptoms. The prescription of harmful drugs is more commonly associated with drugs for occasional use rather than with drugs for chronic conditions. Therefore, a more cautious prescribing of drugs to healthy women in the fertile age is necessary.

Introduction

Since the teratogenic risk of most drugs is still undetermined, it is important to monitor drug use regularly among pregnant women. Drug-utilization studies reveal that most women use drugs during pregnancy, with estimations varying from 44 to 99%[1-2]. However, comparison is difficult because of differences in study design. Interviews or prescription databases may be used for collecting drug-use data, and the type of drugs studied may or may not include over-the-counter (OTC) drugs such as vitamins, iron and analgesics. Most studies found an increasing trend in drug use during pregnancy [2-7].

Drug use cannot be always avoided during pregnancy. For women with certain chronic medical conditions such as epilepsy, diabetes, inflammatory bowel disease and asthma, the use of drugs is essential, and benefits for mother and child may well outweigh the teratogenic risk of the drug [8-9]. Other non-chronic diseases related or unrelated to the pregnancy may require medical treatment. Most studies do not distinguish between the different reasons for which the drugs are prescribed. Therefore, it is not clear to what extent changes in drug use among pregnant women can be explained by chronic, occasional or pregnancy-related drug use.

The aim of this study was to compare the prescription of drugs in pregnant women, with respect to the type of drugs and the fetal risk before, during and after pregnancy.

Methods

This study was performed with the InterAction database (IADB), which contains data on prescriptions dispensed from community pharmacies in the Netherlands. The IADB includes all prescription drugs from an estimated population of 220,000 from 1994 to 1999 and was expanded to approximately 450,000 since 1999 [10-11]. Registration is irrespective of health insurance and is considered representative for the general population. Each prescription record contains information about the drug, date of dispensing, quantity dispensed, dose regimen and the prescribing physician. The indication for the prescription is not known. All the drugs are coded according to Anatomical Therapeutic Chemical (ATC) classification [12]. Each patient has a unique (anonymous) identifier; date of birth and gender of patients are known. Due to a high patient–pharmacy commitment in the Netherlands and sophisticated pharmacy software, the medication records for each patient are virtually complete [13]. The IADB does not include OTC drugs and drugs dispensed during hospitalizations.

To identify mothers, all children born between 1 January 1994 and 1 January 2004 were selected from the database. For each child within the IADB, the female person 15–50 years older than the child with the same address code was considered to be the mother, providing there were no other female persons 15–50 years older with the same address code. Using this method, 65% of the mothers could be identified. Validation of this method is described in detail by Schirm et al [14]. Because only the child's birth date is known, the theoretical conception date was determined as the date of birth minus 273 days (i.e. 9 months). Between 1 January 1994 and 1 January 2004, 10,261 women were identified, with a total of 13,894 pregnancies. To rule out the influence of previous pregnancies, we included only the first pregnancy, as registered in the database, for which complete pharmacy records were available in the IADB from 2 years before the theoretical conception date until 3 months after delivery. According to these criteria, 5,501 women were included. To avoid misclassification of medication use, we subsequently excluded women who gave birth to twins (n = 87) or triplets (n =2) because the gestation period in twin and triplet pregnancies is more likely to be shorter than in singleton pregnancies. Thus, for the final analysis, pharmacy data for 5,412 women were used. To allow direct comparisons of prescription rates over time, the whole study period of 3 years was divided into 12 periods of 13 weeks (trimesters). The 12 trimesters were numbered as can be seen in Figure 1.

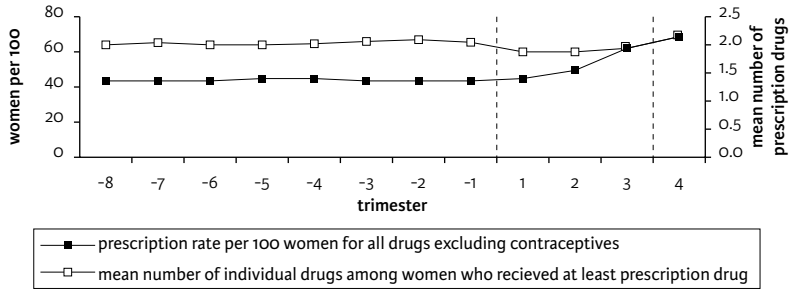

Figure 1: Prescription rate for all prescriptions and the mean number of drugs dispensed among women with at least one prescription. Trimester –8 to –5 represents the second year before pregnancy, trimester –4 to –1 represents the first year before pregnancy. The period between the dotted lines (trimester 1–3) is the pregnancy period, and trimester 4 is the period after pregnancy.

We ordered drugs that were commonly prescribed into three mutually exclusive categories: (1) drugs for chronic conditions, (2) drugs for occasional and short-time use and (3) drugs for pregnancy-related symptoms. Drugs and drug groups belonging to these three categories are listed in Table 1.

Table 1: Categorization of drugs and drug groups included in this study, according to their ATC code

Categories	ATC code
Category I: Drugs for chronic conditions	
Drugs used in diabetes	A10
Corticosteroids, dermatological preparations	D07
Corticosteroids for systemic use	H02
Thyroid therapy	H03
Anti-inflammatory and antirheumatic products	M01
Antimigraine medication	N02C
Antiepileptics	N03A
Antipsychotics	N05A, excl. N05AB04
Antidepressants	N06A
Antiasthmatics	R03
Category II: Drugs for occasional and short-time use	
Antispasmodic and anticholinergic agents and propulsives	A03, excl. A03FA01
Antidiarrhoeals, intestinal anti-inflammatory/-infective agents	A07
Antifungals for dermatological use	D01
Emollients and protectives	D02
Antibiotics and chemotherapeutics for dermatological use	D06
Antiacne preparations	D10
Antibacterials for systemic use	J01
Analgesics and antipyretics	N02B
Anxiolytics	N05B
Hypnotics and sedatives	N05C
Antiparasitic products, insecticides and repellents	P
Antihistamines for systemic use	R06, excl. R06AD & R06AE
Ear, eye, nose and throat preparations	S02, S03, S01, R01, R02A, R05
Category III: Pregnancy-related drugs	
Antacids	A02A
Antiemetics	A03FA01, A04A, N05AB04, R06AD, R06AE
Laxatives	A06
Iron preparations	B03A
Folic acid and derivatives	B03B
Gynaecological anti-infectives and antiseptics	G01
Gonadotrophins and other ovulation stimulants	G03G

The drug categories are mutually exclusive.

Drugs for chronic conditions are not necessarily taken on a chronic basis but can also be taken during episodes when the disease surfaces. The drugs were also classified based on the Australian risk classification for pregnancy (Table 2) [15]. Categories D and X were combined because for both categories, the use of drugs during pregnancy is clearly contraindicated and only one drug was classified as X (isotretinoine, D10BA01). The three B categories were combined for statistical purposes. Drugs that were not classified according to the Australian classification system were categorized as B because their fetal risk was obviously unknown.

Per trimester, we counted the number of specific drugs prescribed to individual women, excluding contraceptives. If a specific drug was prescribed twice during a trimester, it was counted only once. In addition, prescriptions covering more than one trimester were counted only in the trimester in which they were dispensed. The prescription rate was calculated as the number of women per 100 women who received one or more prescriptions for a given drug or drug class within one trimester or otherwise specified time period. Prescription rates were tested in SPSS 12.0.2 for Windows (Chicago, USA) over the 3-year study period and the pregnancy period, using the chi-square test for trend.

Table 2: Risk classification based on the Australian risk classification and as used in this study [15]

A	Drugs that have been taken by a large number of pregnant women and women of childbearing age, without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.	Safe
B	Drugs that have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage or have shown evidence of an increased occurrence of fetal damage, of which the significance is considered uncertain in humans.	Undetermined
C	Drugs that, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate, without causing malformations. These effects may be reversible.	Potentially harmful
D/X	Drugs that have caused or suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.	Harmful

Results

The mean age at birth of the 5,412 mothers included was 29.6 years (range 15–49 years). During the 3-year study period, they received a total of 78,944 drugs, excluding contraceptives, of which 12,407 drugs were dispensed during pregnancy. Overall, 5,236 women (96.7%) received at least one prescription

drug during the 3-year study period and 4,280 (79.1%) received at least one prescription drug during their pregnancy. Figure 1 presents the prescription rates per trimester for all drugs, excluding contraceptives. In the 2 years before pregnancy, the prescription rate was constant, approximately 43 per 100 women. The average number of drugs per trimester among women who were prescribed drugs was two (range 1–17). The prescription rate increased from 43.6 per 100 women in the first trimester to 49.3 and 60.8 per 100 women in the second and third trimester of pregnancy. During pregnancy, the mean number of prescription drugs per trimester among women who were prescribed drugs was approximately the same as before pregnancy (1.9).

During the 3-year study period, 865 different drugs (based on ATC code) were prescribed to our study population, while during the pregnancy period, 470 different drugs were prescribed. The drugs categorized in Table 1 accounted for 57.3% of all the different drugs prescribed and for 81.9% of all prescriptions during the 3-year study period. For the pregnancy period, these were 65.7 and 89.1%, respectively. The prescription rates per trimester for the drugs listed in Table 1 are reported in Appendix 1. A graphical reproduction of the prescription patterns for certain drug groups of the three categories is shown in Figures 2–4.

A clear decrease in prescription rate in pregnancy was seen for antidepressants and antipsychotics (N06A/N05A), antimigraine drugs (N02C; Figure 2), anti-inflammatory and antirheumatic drugs (M01). The prescription rates for antiepileptics (N03A; Figure 2), antiasthmatics (R03) were nearly constant during pregnancy. There seems to be an increase in prescription rate for insulins (A10; Figure 2), but this was not statistically significant.

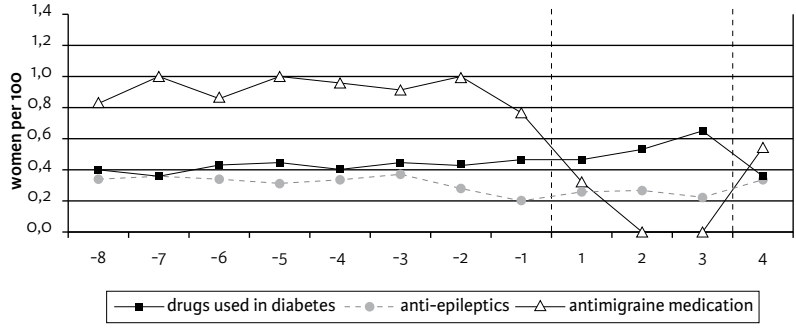

Figure 2: Prescription patterns for certain drugs for chronic conditions in the period from 2 years before pregnancy until 3 months after delivery. The dots represent the prescription rate per trimester for the specific drug class. The period between dotted lines is the pregnancy period. Categorization of drug groups according to Table 1: drugs used in diabetes (A10), antimigraine medication (N02C) and antiepileptics (N03A).

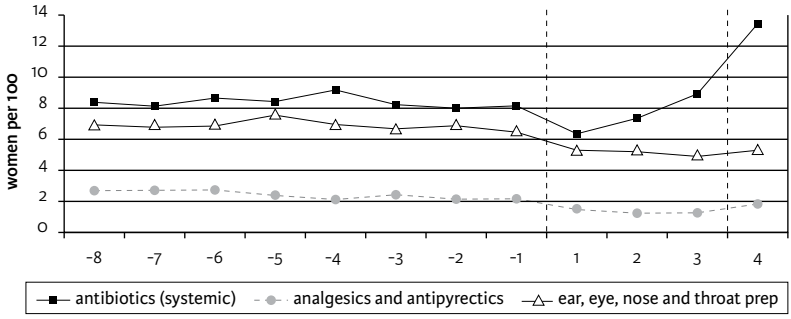

Figure 3: Prescription patterns for certain drugs for occasional and short-time use in the period from 2 years before pregnancy until 3 months after delivery. The dots represent the prescription rate per trimester for the specific drug class. The period between dotted lines is the pregnancy period. Categorization of drug groups according to Table 1: antibacterials for systemic use (J01), analgesics and antipyretics (N02B) and ear, eye, nose and throat preparations (S02, S03, S01, R01, R02A, R05).

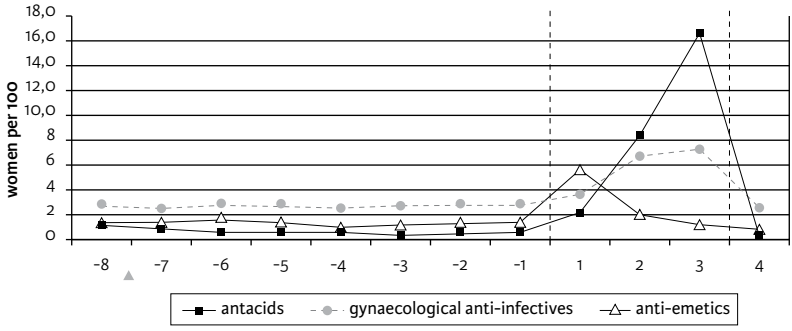

Figure 4: Prescription patterns for certain drugs for pregnancy-related symptoms in the period from2 years before pregnancy until 3months after delivery. The dots represent the prescription rate per trimester for the specific drug class. The period between dotted lines is the pregnancy period. Categorization of drug groups according to Table 1: antacids (A02A), gynaecological anti-infectives and antiseptics (G01) and antiemetics (A03FA01, A04A, N05AB04, R06AD and R06AE).

The prescription rates of drugs for occasional use generally showed a decrease during pregnancy, followed by an increase after delivery. For antibiotics (J01; Figure 3), there was a decrease in prescription rate in the first trimester in pregnancy but an increasing pattern in the second and third trimester. For antispasmodic and anticholinergic agents (A03) and for antihistamines for systemic use (R06), there was a decrease in prescription rate during

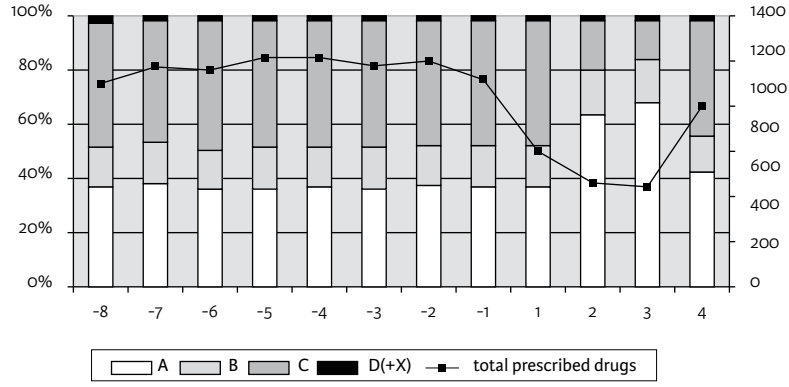

Figure 5: Total number of prescription drugs for chronic conditions (only the prescribed drugs that were categorized as drugs for occasional and short-time use as presented in Table 1 were counted) per trimester and the distribution of these drugs according to the pregnancy risk classification.

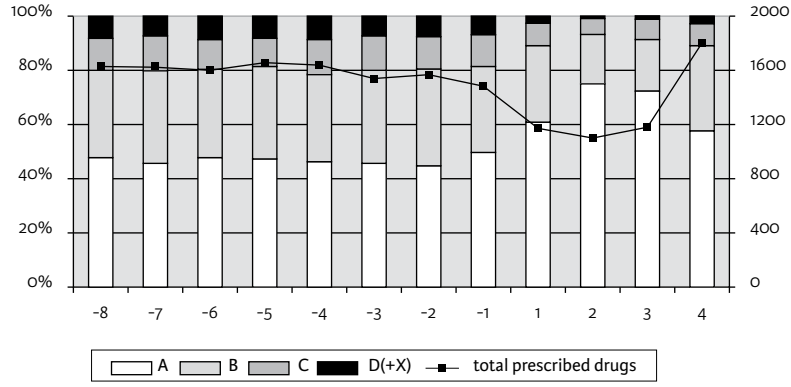

Figure 6: Total number of prescription drugs for occasional and short-time use (only the prescribed drugs that were categorized as drugs for occasional and short-time use as presented in Table 1 were counted) per trimester and the distribution of these drugs according to the pregnancy risk classification.

pregnancy. For analgesics (N02B, Figure 3), hypnotics and anxiolytics (N05C/N05B) and for ear, eye, nose and throat preparations (S02, S03, S01, R01, R02A, R05; Figure 3), there was a decreasing trend during the 3-year period but constant rates during pregnancy. As expected, the prescription patterns of drugs for pregnancy-related symptoms showed an increase during pregnancy.

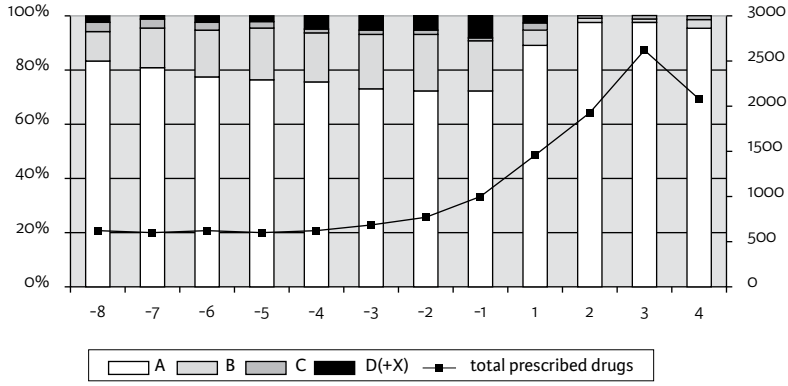

Figure 7: Total number of prescription drugs for pregnancy-related symptoms (only the prescribed drugs that were categorized as drugs for occasional and short-time use as presented in Table 1 were counted) per trimester and the distribution of these drugs according to the pregnancy risk classification.

For folic acid and derivatives (B03B) and for antiemetics (A03FA01, A04A, R06AD, R06AE; Figure 4), the highest rates can be seen in the first trimester. Iron preparations (B03A), antacids (A02A; Figure 4) and gynecological anti-infectives (G01; Figure 4) were most prescribed in the second and third trimester in pregnancy. The prescription of laxatives (A06) was highest after pregnancy. Ovulation stimulants (G03G) were most prescribed before pregnancy, with a prescription rate of 4.2 per 100 women.

Figures 5–7 show the distribution of the fetal risk classification of the prescribed drugs. In these figures, we included only the drugs that were ordered in the three categories according to Table 1. The corresponding numbers can be found in Appendix 2. As previously described, there was a clear decrease in the total number of prescribed drugs for chronic conditions (Figure 5) and for occasional and short-time use (Figure 6) during pregnancy. This decrease was in contrast with the number of prescribed drugs for pregnancy-related symptoms, which showed a large increase during pregnancy, as shown in Figure 7. When taking all categories together, 81.7% of all drugs prescribed during pregnancy were classified as A, 10.9% as B, 6.3% as C and 1.1% as D or X. For the drugs prescribed during the first trimester, these percentages were 70.9, 16.5, 10.2 and 2.4, respectively. However, when we investigated the distribution of the prescribed drugs per category (chronic, occasional or pregnancy related), large differences are observed.

In the first trimester, only 50.4% of the prescribed drugs for chronic diseases were considered safe (A), 30.8% were potentially harmful (C) and 1.7% were classified as harmful (D or X). During pregnancy, the proportion of class A drugs increased to 67% in the third trimester and the proportion

of drugs classified as C decreased to less than 15%. The proportion of harmful drugs was constant (1.9% in the third trimester). After pregnancy, the proportion of potentially harmful and harmful drugs increased to 45%. When we investigated the prescribed drugs for occasional and short-time use, 60.8% of the drugs in the first trimester were classified as safe, 7.8% as potentially harmful and 2.3% as harmful. During pregnancy, the proportion of drugs classified as A increased to over 70% in the second and third trimester. The proportion of harmful drugs decreased to 0.4% in the third trimester. The majority of the drugs prescribed for pregnancy-related symptoms in the first trimester were classified as safe, 2.1% as potentially harmful and 2.9% as harmful. In the second and third trimester of pregnancy, 97.6% of the drugs prescribed for pregnancy-related symptoms were classified as A, 1% as C and 0.2% as D or X.

Discussion

A clear change in drug prescription patterns is visible among pregnant women in the Netherlands. Drugs for chronic conditions and for occasional and short-time use were prescribed less during pregnancy, while at the same time, an increased prescribing of drugs for pregnancy-related symptoms was seen. For all three categories, the proportion of drugs classified as safe increased during pregnancy compared with the period before and after pregnancy.

The prescription rate covering the 3-year study period was very high, with 97 per 100 women receiving at least one prescription drug. The high prescription rate may reflect the origin of our study population. To be included in the prescription database, a person had to purchase at least one prescription drug at a participating pharmacy since 1994. In our population, the prescription rate during pregnancy, including vitamins and iron, was 79%. This percentage is somewhat higher than found in a Dutch cohort of women with a low-risk pregnancy (76.5% of the women attending a gynecologist and 57.4% of the women attending a midwife used medications during pregnancy), but in the latter study, iron supplements were excluded [16]. The prescription rate in this study was high compared with register-based studies in Denmark (44.2%, excluding iron and vitamins), Finland (46.2%) and USA (64%, excluding vitamins and minerals) [1,17-18]. Higher prescription rates during pregnancy were found in the South West of France (99%, including iron and vitamins) and in Germany (96.4 and 85.2%, including and excluding vitamins, respectively) [2,4]. Several explanations can be given for the differences in prescription rates. The Danish study used a database that did not include prescribed drugs that were not refunded, such as benzodiazepines, many analgesics and antacids, explaining the lower prescription rates. Cultural prescribing differences might also play a role in these variations.

Except for drugs used in diabetes, most drugs for chronic conditions were prescribed less during pregnancy. In the trimester after pregnancy,

the prescription rate increased but not to the pre-pregnancy level. Low prescription rates shortly after pregnancy are most likely a result of breastfeeding. For some drugs, such as antidepressants and antipsychotics and antiepileptics, the decrease in prescription rate started before pregnancy. This decrease may indicate precautionary measures by women planning pregnancy, as the safety of these drugs is not established. Several studies have associated the use of antidepressants with adverse pregnancy outcomes such as spontaneous abortions, low birth weight and gestational age [19-20]. From our data, it is not possible to infer whether the decreases are physician driven or woman driven. As the indication for prescription is not known, the possible adverse effects of stopping some of these medications are not known. The prescription rate of antimigraine medication decreased in the second and third trimester of pregnancy, which might be a consequence of less migraine attacks during pregnancy or the use of other analgesics such as paracetamol. Anti-inflammatory and antirheumatic drugs were also rarely prescribed in pregnancy: the use of these drugs is contraindicated in pregnancy and moreover, rheumatic disease activity improves in most women during pregnancy [21].

The prescription of most drugs for occasional and short-time use decreased during pregnancy. The increase in the prescriptions for antibiotics in the second and third trimester can be explained by urinary tract infections, a complication in pregnancy for which treatment is recommended. The high prescription rate of antibiotics after pregnancy is most likely caused by infections of the breast and uterus. Because antibiotics are also frequently prescribed outside pregnancy, we decided to categorize antibiotics as drugs for occasional and short-time use.

The proportion of class A drugs prescribed during pregnancy is somewhat lower than the proportion found in an other study conducted with the IADB (81.7 versus 86%) [6]. This difference can be explained because we restricted our analysis to the drugs that were ordered into the three categories (65.7% of all drugs). In the previous study of the IADB, all drugs were included. The proportion of category A drugs in our study is much higher than found in a Danish study, where 40.9% of all prescriptions during pregnancy were classified as safe (A) [22]. We found that 2.4% of all drugs prescribed in the first trimester were harmful drugs. The harmful drugs prescribed in the first trimester for pregnancy-related symptoms were ovulation-stimulating drugs, and for chronic conditions, antiepileptics. Doxycycline, a tetracycline antibiotic, was responsible for the high percentage of harmful drugs for occasional use in the first trimester. Doxycycline may affect the bone and tooth development of the developing fetus and is therefore contraindicated in pregnancy.

The strength of our study was that for all women included in this study, complete data were available on drugs prescribed in the period from 2 years

before pregnancy until 3 months after delivery. Because we applied a cohort design comparing the prescription rates during pregnancy with the prescription rates before pregnancy in the same population, selection bias is minimized. Some drug-utilization studies compare drug use among pregnant women with drug use among non-pregnant women of comparable age. This might introduce bias, since factors related to pregnancy and drug use might be disproportionately present in the two groups. A Finnish study showed that more non-pregnant women had a chronic disease such as epilepsy, rheumatoid diseases, diabetes, hypertension, ulcerative colitis and psychotic and mental disorders when compared with pregnant women of comparable age [17].

By distinguishing drugs based on their indication, we could demonstrate that the increase in prescription rate during pregnancy is caused by an enhanced prescribing of drugs for pregnancy-related symptoms. Most other drug-utilization studies that investigated drug-use patterns among pregnant women make no distinction between the indications for drug use.

Although our study was conducted with data from a population-based prescription database, only women with a liveborn child are included. Women with a spontaneous or induced abortion and women whose pregnancy resulted in a stillbirth or whose child did not survive until the first prescription were not included.

Since we have no information on the actual length of the gestation period, the time of conception was estimated at 273 days (39 weeks) before birth. The use of a standard gestational period, mostly 270 days, is common in studies using administrative data [4,17-18]. A recent study, comparing administrative data with data from a birth registry, showed that gestational age assumptions can result in a small proportion of misclassification. The extent of potential drug-exposure misclassification was larger for category X drugs in the first trimester of pregnancy [23]. We believe that administrative datasets with estimated gestational age can be useful in research on prescription of drugs during pregnancy. However, in studies evaluating the risk of drugs on birth outcome, precise timing of drug exposure is essential and then administrative datasets alone are insufficient.

In our study, ovulation-stimulating drugs were prescribed in the first trimester of pregnancy, an indication that misclassification has occurred. Prescription of other harmful drugs in the first trimester can also be explained by unawareness of the pregnancy. Although almost 80% of the pregnancies in the Netherlands are planned, a woman mostly does not recognize her pregnancy until the third week after conception.

The prescription rate as defined in this study reflects the prescribing behavior of physicians and cannot be translated directly into exposure rates. Drugs prescribed for a longer period of time can lead to an underestimation of exposure in the subsequent trimesters. Also, particularly in pregnancy, prescribed drugs are not always taken, leading to overestimation of drug

exposure. In a Danish study, only 43% of all drugs dispensed to pregnant women were reported to be taken. Compliance was high for drugs used in chronic diseases but low for drugs used for local or short-time treatment [24]. Furthermore, the prescription database does not include drugs administered in hospitals and OTC drugs. For some drugs, underestimation of exposure may be considerable. The prescription rate of analgesics and antipyretics, for instance, is very low, with approximately 1.5 per 100 women during pregnancy. The number of women who used analgesics during pregnancy is probably much higher because analgesics are freely available in the Netherlands. In a recent study in the USA, where data on maternal drug use were evaluated from two case–control studies of birth defects, at least 65% of the women took paracetamol at some point during pregnancy [25]. Other pregnancy-related drugs such as antacids, laxatives, folic acid and some antiemetics are also available as OTC drugs in the Netherlands.

Although not all drugs prescribed to the study population were ordered into the three categories, we believe that this study is representative for drugs prescribed to pregnant women. The drugs included in the three categories accounted for almost 90% of all prescriptions in the pregnancy period. Drugs not included in the analyses were rarely prescribed.

The use of population-based prescription databases is an important tool to monitor the use of drugs among pregnant women to identify problems. In addition, this individual-level exposure data can serve as a reference for future risk-assessment studies and provide relevant information for education programmes of health professionals as well as for prevention. Although drug use during pregnancy is mostly studied in relation to the occurrence of congenital anomalies at birth, other adverse long-term effects in the offspring, such as developmental delay, may also be associated with maternal drug use in the second and third trimester. In a cohort study in the South West of England, frequent paracetamol use in late pregnancy was associated with an increased risk of wheezing in the offspring at 30–42 months [26]. If maternal drug use can be linked to the prescription of drugs to their children, prescription databases may also be used to screen for certain long-term drug effects.

In conclusion, this register-based study shows that the majority of the Dutch women use drugs during pregnancy. The increase in prescription rate during pregnancy is caused by an increase in prescription rate for drugs used for pregnancy-related symptoms, whereas the prescription rate for drugs for chronic diseases and for occasional and short-time use declines during pregnancy. Also, the prescription of harmful drugs decreases during pregnancy. However, 2.3% of all drugs prescribed for occasional and short-time use in the first trimester were classified as harmful. Therefore, the results of this study argue in favor for a cautious prescribing of drugs to healthy women in the fertile age, in which the prescription of harmful drugs should be avoided as much as possible.

Acknowledgement

We thank M Naunton of the Department of Social Pharmacy, Pharmacoepidemiology and Pharmacotherapy for his thoughtful comments on a previous version of this article.

Appendix 1: Prescription rate per 100 women per trimester* and the results of the chi-square test for trend for all drugs and for the drugs ordered into the three categories

	Trimester												χ^2 test for trend					
													Total period			Pregnancy		
	−8	−7	−6	−5	−4	−3	−2	−1	1	2	3	4	χ^2	*P*	Slope	χ^2	*P*	Slope
All drugs	43.0	43.4	43.3	44.0	44.2	43.0	43.2	43.3	43.6	49.3	60.8	68.0	873.218	0.000	/	320.495	0.300	/
I: Drugs for chronic diseases																		
Drugs used in diabetes (A10)	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.6	0.4	2.126	0.145		1.695	0.193	
Corticosteroids dermatological (D07)	4.7	5.1	4.7	5.1	5.1	4.9	5.2	2.7	3.9	3.5	3.4	4.7	29.701	0.000	\	1.400	0.237	
Corticosteroids systemic (H02)	0.8	0.7	0.8	0.8	0.8	0.7	0.9	0.7	0.4	0.4	0.4	0.6	14.823	0.000	\	0.000	1.000	
Thyroid therapy (H03)	0.7	0.7	0.7	0.8	0.8	0.8	1.0	0.9	0.9	0.9	0.9	1.0	4.930	0.026	/	0.000	1.000	
Anti-inflammatory and antirheumatic drugs (M01)	6.2	6.4	7.1	7.2	7.4	7.1	7.4	6.7	2.2	0.7	0.3	5.0	407.643	0.000	\	86.643	0.300	\
Antimigraine medication (N02C)	0.8	1.0	0.9	1.0	1.0	0.9	1.0	0.8	0.3	0.3	0.0	0.6	42.332	0.000	\	25.607	0.300	\
Antiepileptics (N03A)	0.3	0.4	0.3	0.3	0.3	0.4	0.3	0.2	0.3	0.3	0.2	0.3	1.844	0.174		0.150	0.698	
Antipsychotics and antidepressants (N05A, excl. N05AB04, N06A)	3.0	3.0	2.9	3.1	3.0	2.9	3.2	2.6	1.9	1.5	0.9	2.1	107.641	0.000	\	17.374	0.300	\
Antiasthmatics (R03)	2.4	2.9	2.7	2.9	2.9	2.6	2.5	2.6	2.4	2.4	2.3	2.1	9.788	0.002	\	0.145	0.704	
II: Drugs for short-time and occasional use																		
Antispasmodic and anticholinergic agents and propulsives (A03, excl. A03FA01)	1.6	1.4	1.5	1.5	1.5	1.6	1.3	1.4	0.9	0.3	0.4	0.7	89.387	0.000	\	15.780	0.300	\
Antidiarrhoeals, intestinal anti-inflammatory/anti-infective agents (A07)	0.6	0.7	0.7	0.7	0.7	0.6	0.7	0.6	0.6	0.5	0.6	1.9	16.933	0.000	/	0.017	0.897	
Antifungals for dermatological use (D01)	2.6	2.3	2.4	2.7	2.1	2.4	2.4	2.1	2.6	2.9	3.2	4.7	44.349	0.000	/	3.579	0.059	
Emollients and protectives (D02)	2.0	2.3	1.9	2.0	2.1	1.6	2.0	1.7	2.1	2.3	2.2	2.7	4.457	0.035	/	0.276	0.599	
Antibiotics and chemotherapeutics for dermatological use (D06)	1.3	1.4	1.1	1.1	1.0	1.0	1.0	1.0	0.8	0.7	0.6	1.2	16.963	0.000	\	0.644	0.422	
Antiacne preparations (D10)	1.3	1.4	1.1	1.1	1.0	1.0	1.0	1.0	0.8	0.7	0.6	1.2	9.940	0.002	\	6.557	0.010	\
Antibacterials for systemic use (J01)	8.2	8.0	8.5	8.2	9.0	8.2	7.9	8.1	6.3	7.3	8.8	13.3	19.427	0.000	/	24.448	0.300	/
Analgesics and antipyretics (N02B)	2.4	2.5	2.7	2.1	2.1	2.1	2.0	2.1	1.4	1.1	1.1	1.6	69.431	0.000	\	1.743	0.187	
Anxiolytics, hypnotics and sedatives (N05B, N05C)	2.7	2.9	2.5	2.9	3.2	3.0	2.9	2.6	1.2	0.9	1.5	2.4	66.673	0.000	\	1.797	0.180	
Antiparasitic products, insecticides and repellents (P)	0.7	0.7	0.6	1.0	0.9	0.8	0.9	0.7	0.2	0.1	0.3	0.7	22.614	0.000	\	1.074	0.300	
Antihistamines for systemic use (R06, excl. R06AD and R06AE)	2.2	2.2	1.7	1.9	1.8	2.3	2.2	1.8	1.0	0.4	0.3	1.2	109.604	0.000	\	20.800	0.300	\
Ear, eye, nose and throat preparations (S02, S03, S01, R01, R02A, R05)	6.9	6.7	6.9	7.6	6.9	6.5	6.9	6.4	5.2	5.2	4.8	5.2	63.942	0.000	\	1.111	0.292	
III: Drugs for pregnancy-related symptoms																		
Antacids (A02A)	1.1	0.9	0.6	0.5	0.5	0.4	0.5	0.6	2.1	8.5	16.7	0.5	1533.455	0.000	/	692.835	0.300	/
Antiemetics (A03FA01, A04A, N05AB04, R06AD, R06AE)	1.3	1.4	1.6	1.4	1.0	1.3	1.3	1.4	5.8	2.3	1.1	0.8	24.677	0.000	/	208.959	0.300	\
Laxatives (A06)	1.5	1.8	1.3	1.3	1.3	1.5	1.2	1.5	2.4	2.9	2.8	6.9	334.565	0.000	/	2.018	0.155	
Iron preparations (B03A)	3.2	2.4	1.8	1.5	1.2	1.1	1.2	1.3	5.2	21.3	31.5	30.4	6638.584	0.000	/	1208.418	0.300	/
Folic acid and derivatives (B03B)	1.2	1.5	1.6	2.0	2.4	3.1	4.1	6.1	8.6	3.5	4.7	5.2	460.647	0.000	/	79.302	0.300	\
Gynaecological anti-infectives and antiseptics (G01)	2.6	2.5	2.8	2.7	2.5	2.5	2.7	2.7	3.6	6.5	7.2	2.6	168.624	0.000	/	67.139	0.300	/
Gonadotrophins and other ovulation stimulants (G03G)	0.9	1.0	1.3	1.5	1.9	2.5	2.8	4.2	2.4	0.1	0.1	0.0	25.649	0.000	\	168.553	0.300	\

*Trimester −8 to −5 represents the second year before pregnancy, trimester −4 to −1 represents the first year before pregnancy. Trimester 1–3 is the pregnancy period and trimester 4 is the period after pregnancy.

Appendix 2: Total number of prescription drugs per trimester* and the distribution of these drugs according to the risk classification (only the prescribed drugs that were categorized into drugs for chronic conditions, drugs for occasional use and drugs for pregnancy-related symptoms were included)

	Trimester											
	−8	−7	−6	−5	−4	−3	−2	−1	1	2	3	4
Drugs for chronic diseases												
Total number of prescription drugs	1052	1133	1120	1174	1174	1131	1162	1062	701	536	520	919
Proportion (%) classified as												
A	36.7	38.0	36.2	35.7	36.8	35.9	37.5	36.7	50.4	62.9	67.5	41.8
B	14.5	15.5	14.0	15.5	14.3	15.5	14.1	15.2	17.1	17.4	16.0	13.7
C	46.7	44.5	48.0	47.1	47.4	46.8	47.0	47.1	30.8	17.5	14.6	42.3
D (+X)	2.1	1.9	1.8	1.7	1.4	1.9	1.4	1.0	1.7	2.2	1.9	2.2
Drugs for short-time and occasional use												
Total number of prescription drugs	1632	1628	1587	1651	1636	1553	1573	1497	1166	1109	1186	1805
Proportion (%) classified as												
A	47.9	45.9	48.3	47.6	46.5	45.7	45.5	49.9	60.8	75.1	72.2	58.1
B	32.2	34.3	32.0	33.6	32.4	34.3	35.5	31.5	29.1	18.8	19.4	31.2
C	12.5	13.0	11.8	11.8	12.9	13.1	12.1	12.6	7.8	5.5	8.0	8.6
D (+X)	7.4	6.7	7.9	7.1	8.2	6.9	6.9	5.9	2.3	0.5	0.4	2.1
Drugs for pregnancy-related symptoms												
Total number of prescription drugs	593	573	588	570	594	659	748	975	1433	1913	2612	2051
Proportion (%) classified as												
A	83.0	80.6	77.7	76.7	75.1	73.0	72.1	72.4	89.2	97.6	97.6	95.3
B	11.6	14.7	17.3	18.8	18.7	20.3	21.0	18.5	5.9	1.2	1.3	3.7
C	3.4	3.5	2.7	2.6	1.9	1.8	2.1	1.5	2.1	1.0	1.0	1.0
D (+X)	2.0	1.2	2.2	1.9	4.4	4.9	4.8	7.6	2.9	0.2	0.1	0.0

*Trimester −8 to −5 represents the second year before pregnancy, trimester −4 to −1 represents the first year before pregnancy. Trimester 1–3 is the pregnancy period and trimester 4 is the period after pregnancy.

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2 DIFFERENCES IN ANTIEPILEPTIC DRUG USE DURING PREGNANCY IN THREE EUROPEAN COUNTRIES

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Background: Among malformed pregnancy outcomes the distribution of the type of antiepileptic drug exposure varies between countries in the EUROCAT *Antiepileptic Study Database.* However data of antiepileptic drug exposure in the general pregnant population is scarce.

Objective: To identify antiepileptic drug utilization patterns in pregnancy in European countries using prescription databases.

Methods: Data of population-based prescription databases is used. Included were the region of Midi-Pyrenees in France (June 2003-June 2008) based on the '*French Health Insurance Service'*, the region of Emilia Romagna (2003-2007) based on a linkage between the Regional Health authority database and the birth database and the northern part of the Netherlands (2003-2008) using the *IADB.nl* based on data of community pharmacies.
Antiepileptic drug exposure was defined as at least 1 prescription for any Antiepileptic drug (atc N03A) irrespective of indication.

Results: In total 83,005 French, 185,133 Italian and 13,036 Dutch pregnancies were included. The exposure to antiepileptic drugs before pregnancy is higher in France (7/1000) compared with Italy and the Netherlands (4/1000). However in pregnancy all regions have exposures around 2 to 3/1000. In the Netherlands about 60% of all antiepileptic drug exposed pregnancies used valproic acid or carbamazepine, this is around twice as much as in France. The use of clonazepam and lamotrigine is more common in France and the use of phenobarbital and gabapentine in Italy.

Conclusions: Teratogenicity is expected to be comparable within Europe, but the use of Antiepileptic drugs in the general pregnant population in France, Italy and the Netherlands is not similar.

Introduction

Although, the majority of antiepileptic drugs are known teratogens, most women need to continue their drug use during pregnancy.

In earlier studies with the EUROCAT congenital anomalies registries we found that the type of antiepileptic drugs used in pregnancies (with a malformed outcome) varied between countries (unpublished data). We wondered if this dissimilarity was a coincidence due to small numbers, or if it was due to different treatment practices and therefore, different use among the general fertile population in European countries.

In literature several reports can be found about antiepileptic drug treatment in the general non-pregnant population [1-3]. The estimates of the prevalence of antiepileptic drug use vary widely between 0.8 and 5.2% in adults. Epilepsy is the most common indication, although antiepileptic drugs are more frequently prescribed for other indications, such as pain or mood disorders [2-3]. Especially, in the countries with higher prevalences the use for other indications is more prevalent. The therapy of some of these other indications can be discontinued if a women wishes to become pregnant. Additionally, the use of antiepileptic drugs increases with age; among women in the fertile age 25-44 the prevalence of antiepileptic drug use is estimated at 7.2 per 1000 in Denmark [1].

In the Netherlands and Norway population based drug utilization studies are available for exposure around pregnancy. The use of antiepileptic drugs in these studies during pregnancy was 3 per 1000, but no information was available from these studies on the use of specific antiepileptic drugs [4-5].

From pregnancy registries we know that carbamazepine, lamotrigine and valproic acid are in various orders the most commonly used antiepileptic drugs in pregnancy. Noteworthy, is the increasing trend of the prevalence of lamotrigine and the decreasing trend of carbamazepine and valproic acid in recent years [6-7].

European population-based data including information about specific antiepileptic drug exposure around pregnancy is scarce and therefore our objective is to describe and compare the maternal exposure to specific antiepileptic drugs (before and) during pregnancy in France, Italy and the Netherlands.

Methods

Databases

For this study we included three regions in three countries. In the three datasets drug information is available, although no information is available on the indication of prescribing the antiepileptic drugs.

The French data is based on the 'French Health Insurance Database' for the region Midi Pyrénées (2.8 million inhabitants) including babies born from June 2003 to May 2004 and 2007. For July 2004-2006 and January 2008 to June 2008 only data of Haute Garonne (1.1 million inhabitants) are included which is part of the region of Midi Pyrénées. About 80% of all inhabitants are insured by

this health insurance company, mainly farmers and civil servants are insured by another organization and therefore not included. In France, women have to declare their pregnancy to the Health Insurance System before the end of the third month of pregnancy in order to receive full reimbursement of care and all reimbursed drugs from the 6th month of pregnancy. Information is available for all out-patient prescribed drugs. Both the first day of the last menstrual period and the data of delivery are known by the Health organization.

The Italian data from the region of Emilia Romagna (4 million inhabitants) is derived from a linkage of the Regional Health authority database (including drug prescription data) with the birth database (containing information about pregnancies). Linkage was based on personal fiscal code. Data is available for 2003-2007. Information is available for all out-patient prescribed antiepileptic drugs and the first day of the last menstrual period is known.

For the Netherlands we used data of the IADB.nl.: a community pharmacy prescription database including pregnancies. This database holds the prescription history for 500,000 people in the Northern Netherlands and is described and validated earlier [4,8]. Dutch data is included for pregnancies ending from 2003 to 2008. Information is available for all out-patient prescriptions. The first day of the last menstrual period is unknown, but estimated as 273 days before the delivery date.

Analyses & Statistics

All prevalences presented are based on prescription data, not on verified use. Prevalences are calculated as the total number of individual women with at least 1 prescription per trimester divided by the total number of pregnancies included. Trimesters were defined as a period of 91 days. If a specific antiepileptic drug was prescribed twice in a trimester it was counted only once and if a prescription covered a longer time period than one trimester it was only counted in the trimester in which the prescription was dispensed. Polytherapy is defined as at least two different antiepileptic drugs (based on atc-code) received in one trimester. It is not possible to receive a prescription for a period longer than our defined trimester in one of the included countries.

Results

In total 83,005 French, 185,133 Italian and 13,036 Dutch pregnancies were available for analysis (see table 1). The French women were slightly older than the Dutch women (not significant) and the age of the Italian women lies in between them. More women in France compared to Italy and the Netherlands had at least one prescription for any antiepileptic drug during pregnancy (5.2 versus 4.0 and 4.2 per 1000, France versus Italy $p<0.01$). The proportion of mono and poly therapy varied between 11% in the Netherlands, 14% in Italy and 16% in France. The antiepileptic drug combinations in the poly therapy varied both within and between regions.

Table 1: Characteristics of the study population

region, country	Northern Netherlands	Midi Pyrenee, France^	Emilia Romagna, Italy
included years	2003-2008	2003-2008	2003-2007
total pregnancies	13,036	83,005	185,133
age of mother at birth	30.9 (21-49)	31.7 (18-44)	31.23 (18-61)
prevalence any AED*	4.1/1000	5.2/1000	4.0/1000
mono	89%	84%	86%
poly 2 AEDs#	11%	14%	11%
poly 3 AEDs#	0%	2%	3%

** prevalence of antiepileptic drugs calculated as women with at least 1 prescription during pregnancy.*

 # poly 2/3 AEDs= at least 1 prescription of 2/3 different antiepileptic drugs in 1 trimester.

^ Midi Pyrénées: from 06-'03 to 05-'04 and 2007. Haute Garonne only: from 07-'04 to 12-'06 and 01-'08 to 06-'08.

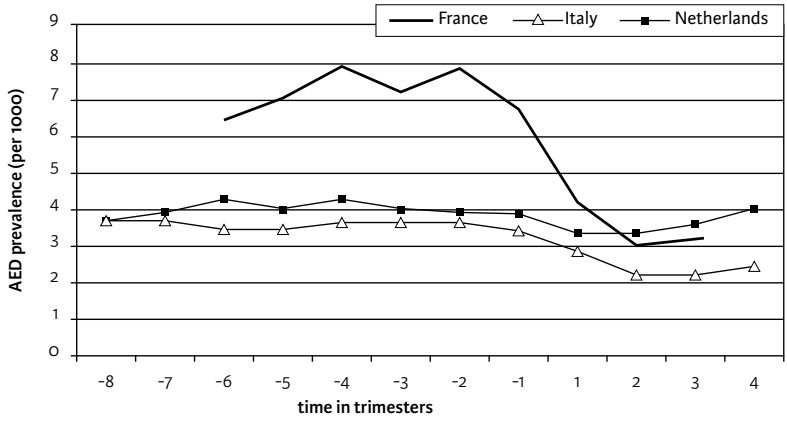

Figure 1: Prescription rate for any antiepileptic drug (prevalence per 1000) per region.

In *figure 1* the prescription rate for any antiepileptic drug is presented per region. Data for France were available from one and a half year before pregnancy until delivery and the Italian and Dutch data were available from two years before pregnancy until three months after delivery. As you can see the prescription rate over time is lower and much more stable in Italy and the Netherlands compared to France. All three countries show a drop in the prevalence towards the beginning of pregnancy however this drop is much bigger in France. Italy has the lowest prevalence of the three regions during pregnancy.

Figure 2 shows the trend over years in the use of antiepileptic drugs during pregnancy in the different regions. For the first generation antiepileptic drugs the exposure to valproic acid and especially carbamazepine is much

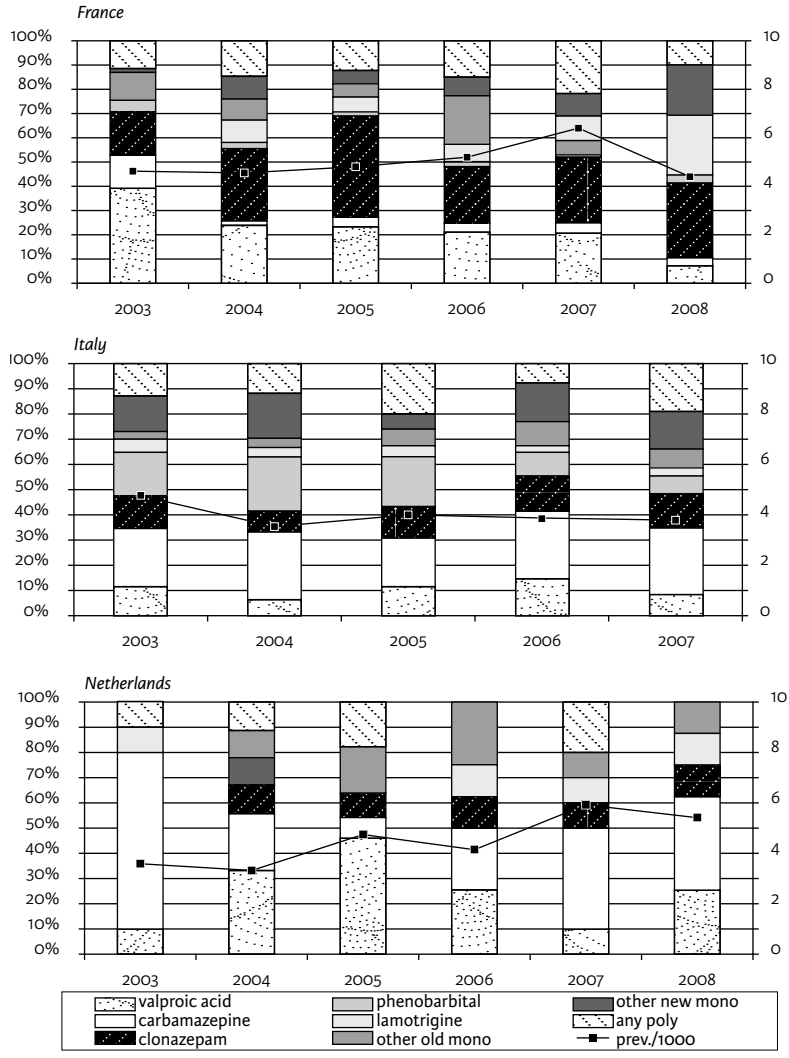

Figure 2: Time trends in the prevalence of antiepileptic drug use during pregnancy (line) and specific types of antiepileptic drugs (bars) in France, Italy and the Netherlands

higher in the Netherlands than in France or Italy. The other way around clonazepam exposure is much more frequent in France and phenobarbital is more frequent used in Italy. Lamotrigine is in France and the Netherlands the most used second generation antiepileptic drug. The first lamotrigine prescriptions appeared in the Netherlands in 2003 and in France in 2004.

However the exposure rate is higher in France. In Italy gabapentine is the most frequently used second generation antiepileptic drug during pregnancy. The prevalence of gabapentine decreases towards more recent years probably due to the increase of pregabaline use (presented in the graph as 'other new monotherapy).

The prevalence of antiepileptic drug exposure remains more or less stable over time in France and Italy, but in the Netherlands it seems that exposure increases in the more recent years however this is not statistically significant (line in *Figure 2*). This increase in the Dutch prevalence remains if the study period is enlarged to 1995-2009 (data not shown).

Discussion

The prescribed antiepileptic drugs around pregnancy are not similar for France, Italy and the Netherlands. The prevalence for any antiepileptic drug exposure during pregnancy is higher in France than in Italy and the Netherlands, respectively 5.2, 4.0 and 4.2 per 1000. Next to this the types of drugs prescribed are different too. Remarkable is the large proportion of clonazepam use in France, the use of phenobarbital in Italy and carbamazepine in the Netherlands.

Policy & Literature

A French population-based study in Béziers estimated an antiepileptic drug exposure prevalence of around 8 per 1000 in women 20-40 years [9]. This seems to be in line with the prevalence we found for France before pregnancy. In France it seems more common to reconsider the need for antiepileptic drugs before or in the beginning of the pregnancy and after this reconsidering process both regions in France and Netherlands end up with a comparable prevalence of antiepileptic drug exposure of 3 per 1000. The Italian prevalence is somewhat lower; 2 per 1000 ($p<0.01$).

In a French survey (2003) epileptologists were asked which antiepileptic drug they found most appropriate for newly diagnosed women of childbearing age considering pregnancy and those not considering pregnancy [10]. For all types of epilepsy included in the survey lamotrigine was considered to be the most appropriate drug for women considering pregnancy with valproic acid as an overall drug of second choice. In women not considering pregnancy it is the other way around: valproic acid is the most appropriate followed by lamotrigine. In both groups of women, carbamazepine is only an appropriate choice according to the epileptologists in case of symptomatic or cryptogenic partial epilepsy. This explains the small proportion of carbamazepine in France compared to the proportion in the Netherlands and the decreasing trend of valproic acid and the increasing trend of lamotrigine. However,

based on this survey the proportion of lamotrigine exposure might be expected higher in our study, but this survey was based on newly diagnosed patients. As switching between antiepileptic drugs is not usual in case of good control the young women receiving lamotrigine are maybe not pregnant yet (lamotrigine got market approval in 1995 in France). The proportion of lamotrigine exposure in pregnancy is expected to increase further in future. Remarkable is the proportion of clonazepam exposure in pregnancy in our study (almost 30%). In particular as the epileptologists in the survey reported that this drug is 'sometimes useful in case of failure or contraindication of the other antiepileptic drugs'. However in practice it seemed to be considered safer than other antiepileptic drugs and it seems to be used in the treatment of depression.

Two studies estimating the use of antiepileptic drugs in Italy in the general non-pregnant population including men and women of all ages (both study periods 2003-2005) show a similar top 3 of antiepileptic drug use: phenobarbital, carbamazepine and valproic acid [11-12]. In our study carbamazepine is the most used antiepileptic drug during pregnancy followed by phenobarbital and clonazepam and valproic acid as a number 4 (see figure 2). The median age of phenobarbital users was relatively high: 58 years in at least one of the two studies [11]. This might explains why in a pregnant population the proportion of phenobarbital is somewhat lower. However, compared to France and the Netherlands the phenobarbital use is still very high. Like in France it is remarkable to find a high proportion of clonazepam exposure during pregnancy compared to the use found in literature. The clonazepam used by Italian women in this study is mainly used for the treatment of depression.

Of the second generation antiepileptic drugs gabapentine is both in our study and in the two studies performed in the general population the most frequently prescribed drug [11-12].

For the Netherlands valproic acid and carbamazepine were the two drugs of first choice in case of partial epilepsy. However in 2009 lamotrigine changed from a second to a first choice option for this type of epilepsy. For generalized epilepsy the only first choice option is valproic acid [13]. This explains why over 65% of all monotherapy exposed pregnancies were exposed to valproic acid or carbamazepine in our study period. The prevalence of lamotrigine will probably increase in future due to this change in guidelines and the fact that potential teratogenicity gets more attention. The use of antiepileptic drugs for other indications than epilepsy seems to be less frequent in the Netherlands (although we do not know the indication in our data). In particular clonazepam is not registered for depression in the Netherlands [13].

Strengths & Limitations

As far as we know this is the first population-based drug utilization study presenting the type of antiepileptic drug use around pregnancy for several European regions.

This study is based on prescription data and we therefore cannot be sure if the drugs are really taken by the women. 'Only' 4-5 per 1000 pregnancies are exposed to antiepileptic drugs and therefore despite the large number of pregnancies included we still have small numbers for the individual drugs. Another limitation is that we do not know the first day of the last menstrual period for the Dutch data. We estimated each pregnancy to last 273 days. However, as antiepileptic drugs mainly are used chronically we do not expect a major bias.

Daily practice

The use of antiepileptic drugs varies between the included regions, however the teratogenicity can be expected to be comparable within these western European countries (maybe except for influence of epigenetic differences). As local guidelines for treatment around pregnancy should be based on all evidence available world-wide we expected to find fewer differences in actual use between France, Italy and Netherlands. Although, it is of course known that keeping daily practice in concordance with constantly updating scientific knowledge is hard [14-15].

From earlier studies we know that valproic acid seems to be the most teratogenic antiepileptic drug [16]. In 2009, the American Academy of Neurology advised to avoid valproic acid in pregnancy if possible [*17*]. Carbamazepine seems to be relatively safe [18] and although there is less experience up to now lamotrigine also does not seem to be very strongly related to a specific malformation (except for an indication for an association with club foot) [19-20]. Based on this information one would expect to see relatively large proportions of carbamazepine and lamotrigine during pregnancy in the near future. However, antiepileptic drugs are used for complex diseases for which the therapy choice can only be made on individual basis. Additionally, although if possible valproic acid should be avoided during pregnancy still the majority of children are born without malformations. Although, a less clear figure exists of the behavior problems, (possibly) related to valproic acid, such as mental retardation and cognitive development [21-22].

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Part II

Risk assessment of antiepileptic drugs in the first trimester of pregnancy

3 DOES LAMOTRIGINE USE IN PREGNANCY INCREASE OROFACIAL CLEFT RISK RELATIVE TO OTHER MALFORMATIONS?

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Neurology 2008;71:714-722

Objective: To investigate whether first trimester exposure to lamotrigine monotherapy is specifically associated with an increased risk of orofacial clefts relative to other malformations, in response to a signal regarding increased orofacial cleft risk.

Methods: Population-based case-control study with malformed controls based on EUROCAT congenital anomaly registers. The study population covered 3.9 million births from 19 registries 1995–2005. Registrations included congenital anomaly among livebirths, stillbirths, and terminations of pregnancy following prenatal diagnosis. Cases were 5,511 nonsyndromic orofacial cleft registrations, of whom 4,571 were isolated, 1,969 were cleft palate and 1,532 were isolated cleft palate. Controls were 80,052 nonchromosomal, non-orofacial cleft registrations. We compared first trimester lamotrigine and antiepileptic drug (antiepileptic drug) use versus nonepileptic non-antiepileptic drug use, for mono and polytherapy, adjusting for maternal age. An additional exploratory analysis compared the observed and expected distribution of malformation types associated with lamotrigine use.

Results: There were 72 lamotrigine exposed (40 mono- and 32 polytherapy) registrations. The odds ratios for lamotrigine monotherapy versus no antiepileptic drug use were 0.67 (95%CI 0.10–2.34) for orofacial cleft relative to other malformations, 0.80 (95%CI 0.11–2.85) for isolated orofacial cleft, 0.79 (95%CI 0.03–4.35) for cleft palate, and 1.01 (95% CI 0.03–5.57) for isolated cleft palate. odds ratios for any antiepileptic drug use versus no antiepileptic drug use were 1.43 (95% CI 1.03–1.93) for orofacial cleft, 1.21 (95%CI 0.82–1.72) for isolated orofacial cleft, 2.37 (95%CI 1.54–3.43) for cleft palate, and 1.86 (95%CI 1.07–2.94) for isolated cleft palate. The distribution of other nonchromosomal malformation types with lamotrigine exposure was similar to non-antiepileptic drug exposed.

Conclusion: We find no evidence of a specific increased risk of isolated orofacial clefts relative to other malformations due to lamotrigine

monotherapy. Our study is not designed to assess whether there is a generalized increased risk of malformations with lamotrigine exposure.

Introduction

Post marketing surveillance of the second generation antiepileptic drug (antiepileptic drug) lamotrigine (lamotrigine) during pregnancy has recently generated a signal regarding higher risk of orofacial clefts (orofacial clefts) based on data from the North American antiepileptic drug Pregnancy Registry. They reported an unexpectedly high prevalence of isolated nonsyndromic, orofacial clefts in infants exposed to lamotrigine monotherapy during the first trimester of pregnancy: 3 isolated cleft palate (cleft palate) and 2 isolated cleft lip with or without palate were identified among 564 exposed pregnancy outcomes, a rate of 8.9 per 1,000[1]. These results were followed by a Food and Drug Administration (FDA) alert [2]. Three other registries have reported one or two cases of orofacial cleft, and one none, but have not provided enough evidence to confirm or refute the orofacial cleft signal [3-7].

Case-control studies are recommended to test signals emanating from pregnancy registers [8]. The EUROCAT network of population-based congenital anomaly registers covers more than one quarter of births in Europe, following standardized methodology and contributing to a central database [9-10]. We report a case-control study, with malformed controls, to assess whether first trimester exposure to lamotrigine monotherapy versus nonepileptic non-antiepileptic drug use is specifically associated with an increased risk of orofacial cleft relative to other malformations. We also report an exploratory analysis of the types of malformations associated with lamotrigine exposure, comparing them to what would be expected in a nonepileptic non-antiepileptic drug exposed population.

Method

Study population and database.

The EUROCAT central database holds individual standardized records of congenital anomaly registrations since 1980 including livebirths, stillbirths, and terminations of pregnancy following prenatal diagnosis. The standard data on each registration are described in EUROCAT Guide 1.3 [10]. One syndrome and up to eight malformations are coded by ICD9 or ICD10 codes. Babies with only anomalies on the EUROCAT list of minor anomalies are excluded [10]. Other variables include date of birth, pregnancy outcome (live, still, termination), maternal age, maternal disease before and during pregnancy (ICD coded + text), and drugs taken in the first trimester of pregnancy. Up to 2004 (birth year), registries could give up to three drug codes

(grouped into 20 categories) as well as text information on the drug [11]. From 2005, and for some registries before 2005, drugs are coded according to the Anatomic Therapeutic Chemical (ATC) classification [12]. Information about maternal drug exposure is mainly obtained from obstetric records, and some registries also use maternal interviews after birth or linkage with pharmacy databases [11].

Table 1: Participating registries, study years, number of births surveyed, number and prevalence of orofacial clefts (orofacial cleft), and number of controls.

Registry	years	total births	Orofacial cleft cases		Controls#
			number	prevalence*	number
Antwerp, Belgium	97 - 05	162,545	246	1.51	3,491
Basque Country, Spain	95 - 05	193,037	137	0.71	2,576
Cork & Kerry, Ireland	96 - 03	63,007	73	1.16	1,262
Emilia Romagna, Italy	00 - 04	140,726	108	0.77	2,054
Hainaut, Belgium	97 - 05	110,557	153	1.38	2,354
Mainz, Germany	96 - 04	29,859	61	2.04	1,220
Malta	96 - 04	38,495	58	1.51	1,180
Northern Netherlands	95 - 05	216,940	377	1.74	3,921
Norway	99 - 05	406,805	728	1.79	13,440
Odense, Denmark	95 - 04	55,677	104	1.87	1,063
Paris, France	97 - 05	347,778	381	1.10	9,192
Poland	99 - 04	1,189,902	1,744	1.47	15,739
Saxony Anhalt, Germany	96 - 05	146.511	303	2.07	4,115
Strasbourg, France	97 - 02	80,919	117	1.45	2,053
Tuscany, Italy	02 - 05	112,684	107	0.94	1,891
Vaud, Switzerland	97 - 05	65,339	69	1.06	2,070
Wales, UK	98 - 05	255,077	360	1.41	7,872
Wielkopolska, Poland	99 - 04	206,481	320	1.55	3,780
Zagreb, Croatia	95 - 04	59,253	65	1.10	779
Total	95 - 05	3,881,592	5511	1.42	80,052

** Prevalence of orofacial cleft per 1000 births*

 # Controls: all non chromosomal, non orofacial cleft, registrations

Criteria for registries to participate in the study were as follows:

1. Maternal epilepsy or antiepileptic drug exposure recorded for at least 3 per 1,000 registrations for the study period. This criterion was set a priori based on population information on epilepsy prevalence to exclude registries with low ascertainment of epilepsy.
2. Specific drug name or complete seven-digit ATC code available for at least 80% of antiepileptic drug exposed babies/fetus for the study period.

Nineteen registries met these criteria. The study period for each registry (table 1) started in or after the year of lamotrigine licensing in the country.

The study population comprised a total of 3,881,592 births. The total number of congenital anomaly registrations in the study population was 98,075, of which 11,784 were chromosomal and 86,291 nonchromosomal.

Part I: Case-control study

Study design
Population-based case-control study, with malformed controls. Odds of lamotrigine exposure among orofacial cleft registrations (cases) was compared with the odds of lamotrigine exposure among malformed non-orofacial cleft registrations (controls).

Case definition
Livebirths, fetal deaths from 20 weeks, and terminations of pregnancy following prenatal diagnosis with nonchromosomal orofacial clefts. The primary hypothesis concerned isolated orofacial cleft, the subject of the FDA alert, and secondary hypotheses concerned isolated cleft palate, which carried a higher relative risk than cleft lip in the original signal, and a wider definition of nonsyndromic orofacial cleft and cleft palate, including multiply malformed cases [1-2].

Monogenic syndromes (n=163) were excluded. Also excluded were cases where orofacial cleft was secondary to another primary anomaly (n=345) such as holoprosencephaly or Pierre Robin sequence. Isolated (I) orofacial clefts were designated by a panel of three medical geneticists, blind to exposure status, to include only those orofacial clefts without another anomaly, or with only a minor or unspecified anomaly, or an anomaly forming part of the orofacial cleft malformation [10].

Control definition
Livebirths, fetal deaths from 20 weeks gestation, and terminations of pregnancy following prenatal diagnosis, with nonchromosomal, non orofacial cleft, major defects.

Exposure definition
Registrations with coded maternal epilepsy or antiepileptic drug exposure (whether for epilepsy or not) were extracted from the database, and verified with participating registries. Exposures were classified as monotherapy versus polytherapy (use of two or more drugs in the first trimester), and by type of antiepileptic drug (lamotrigine, valproic acid, carbamazepine, other). After verification with registries, 98.9% of antiepileptic drug exposures were of known drug name. To avoid misclassification we excluded epileptic mothers without recorded antiepileptic drug exposure from both cases and controls (9 cases, 185 controls). An additional 5 case and 21 control mothers were

excluded (mothers with childhood epilepsy or epilepsy prior to pregnancy or unconfirmed epilepsy without antiepileptic drug use).

Statistical analysis

Crude odds ratios were calculated ignoring the registry of origin. In order to analyze the data taking into account the registry and including all registries (even if they had no exposure to lamotrigine in either cases or controls) the WinBUGS computer package was used to fit multinomial responses with a logistic link. Maternal age was treated as a categorical variable (<20, 20–24, 25–30, 30–35, and 35> years of age). Due to the small numbers of exposures to lamotrigine it was not possible to adjust simultaneously for both registry and maternal age. Odds ratios are equivalent to a relative risk where the outcome is rare.

Statistical power

We designed the study to answer the concern raised by the FDA alert regarding an observed relative risk of isolated orofacial clefts of approximately 17 relative to a generally raised risk of other malformations1-2. We estimated with the EUROCAT population expected to be available for study, and the estimated exposure rate, 80%power and p0.05, that the study could detect an odds ratio of 5 for isolated orofacial clefts and 10 for isolated cleft palate, i.e., enough power to confirm or refute an excess of the size of the original signal. The final study population was larger than estimated, giving a higher power.

Table 2: Antiepileptic drug (antiepileptic drug) exposure among registrations*

	number	Per 1,000 registrations N= 85,563
Any antiepileptic drug	495	5.79
Any antiepileptic drug monotherapy	409	4.78
Valproic acid monotherapy	181	2.12
Carbamazepine monotherapy	125	1.46
Lamotrigine monotherapy	40	0.47
Other monotherapy*	63	0.74
Any antiepileptic drug polytherapy	86	1.01
Including valproic acid	57	0.67
Including carbamazepine	39	0.46
Including lamotrigine ***	32	0.37
Other polytherapy****	4	0.05

* *Registrations include cases of orofacial cleft and controls (other malformations) as defined in the Methods section.*

** *26 phenobarbital, 9 oxcarbazepine, 7 clonazepam, 5 phenytoin, 3 primidon, 3 topiramate, 2 methylphenobarbital, 1 levetriacetam, 1 ethosuximide, 6 unspecified*

*** *22 out of 32 of lamotrigine polytherapy included valproic acid and 8 out of 32 included carbamazepine*

**** *polytherapy without valproic acid, carbamazepine or lamotrigine*

Part II: Exploratory hypothesis-generating analysis.
An exploratory hypothesis-generating analysis compared the proportion of different malformation subgroups, according to EUROCAT subgroup definitions, among all nonchromosomal registrations, between lamotrigine exposed (all and mono) and antiepileptic drug unexposed registrations. Exclusions were the same as for the case-control analysis [10].

A further analysis compared the proportion of chromosomal registrations among lamotrigine exposed and antiepileptic drug unexposed registrations, controlling for maternal age in 5-year age groups. Assuming no relationship between exposure and chromosomal anomaly risk, we would expect a lower proportion of chromosomal registrations if the risk of nonchromosomal anomalies was raised.

Ethics approval: approved by the University of Ulster Ethics Committee.

Results

Case-control study
A total of 85,563 registrations comprising 5,511 orofacial cleft cases and 80,052 non-orofacial cleft controls were eligible for the case-control analysis (table 1). Of the 5,511 orofacial cleft cases, 4,571 were isolated, and 1,969 had cleft palate of whom 1,532 were isolated.

There were 495 antiepileptic drug exposed cases and controls (table 2) or 5.8 per 1,000 registrations. Seventeen out of 495 had no recorded maternal epilepsy, of which 1 was exposed to lamotrigine. Over 80%, 409 out of 495, of these antiepileptic drug exposed mothers used monotherapy (table 2). There were 72 lamotrigine exposed cases and controls of which 56% (40/72) were lamotrigine monotherapy (table 2). The proportion of antiepileptic drug exposed registrations declined over time (table 3) while the proportion of lamotrigine exposure per 1,000 registrations doubled from 0.5 in 1995–1998 to 1.1 in the period 2002–2005 (table 3). The proportion of lamotrigine use among all antiepileptic drug use grew from 7.3% (6/82) in 1995–1998 to 20.5% (45/219) in the period 2002–2005 (table 3).

Antiepileptic drug exposed registrations were similar in maternal age to non exposed (28.8 versus 28.9 years), but lamotrigine exposed tended to be younger: 26.8 years for monotherapy and 27.8 for polytherapy. orofacial cleft cases had a similar mean maternal age to controls, but more detailed analysis shows a slightly higher risk of orofacial cleft in young mothers [13].

As expected given the types of anomalies, there were more terminations of pregnancy following prenatal diagnosis among controls (5,718/80,052 or 7.1%) than among orofacial cleft cases (159/5,511 or 2.9%). The proportion of fetal deaths was similar between controls (1.3%) and cases (1.4%). The proportion of antiepileptic drug exposure was 5.6 per 1,000 registrations

Table 3. Year of birth of registrations* by case and exposure status

		Cases						Exposure					
	Registrations	Orofacial Cleft			Cleft palate			Any AED			Lamotrigine		
year of birth	No.	I	M	I+M per 1000 reg	I	M	I+M per 1000 reg	mono	poly	Any AED per 1000 reg	mono	poly	Any lamotrigine per 1000 reg
95-98	11582	542	109	56.2	156	40	16.9	70	12	7.1	2	4	0.5
99-01	30952	1748	367	68.3	577	179	24.4	166	28	6.3	10	11	0.7
02-05	43029	2281	464	63.8	799	218	23.6	173	46	5.1	28	17	1.1

I: Isolated, M: Multiply malformed, mono: monotherapy, poly: polytherapy

**Registrations (Reg) include cases of orofacial cleft and controls (other malformations) as defined in the Methods section.*

Table 4: Orofacial Cleft (orofacial cleft) odds ratios (OR) for AED and lamotrigine exposure compared to no AED exposure

		Isolated orofacial cleft n=4571	Isolated & mult. orofacial cleft n=5511	Isolated CP n=1532	Isolated & mult. CP n=1969
No AED		4540 1.0	5467 1.0	1516 1.0	1943 1.0
Any AED	Number OR ORadjusted	31 1.21 [0.81-1.74] 1.21 [0.82-1.72]	44 1.42 [1.02-1.94] 1.43 [1.03-1.93]	16 1.86 [1.05-3.07] 1.86 [1.07-2.94]	26 2.36 [1.52-3.52] 2.37 [1.54-3.43]
Any AED monotherapy	Number OR ORadjusted	26 1.23 [0.79-1.83] 1.23 [0.81-1.79]	37 1.45 [1.00-2.04] 1.46 [1.02-2.02]	15 2.12 [1.17-3.55] 2.11 [1.20-3.42]	23 2.53 [1.58-3.87] 2.55[1.61-3.77]
Any AED polytherapy	Number OR ORadjusted	5 1.11 [0.35-2.70] 1.04 [0.37-2.40]	7 1.29 [0.50-2.79] 1.24 [0.51-2.57]	1 0.66 [0.02-3.82] 0.48 [0.02-2.58]	3 1.56 [0.31-4.72] 1.41 [0.32-3.94]
Lamotrigine monotherapy	Number OR ORadjusted	2 0.92 [0.11-3.57] 0.80 [0.11-2.85]	2 0.77 [0.09-2.97] 0.67 [0.10-2.34]	1 1.38 [0.03-8.19] 1.01 [0.03-5.57]	1 1.08 [0.03-6.39] 0.79 [0.03-4.35]
Lamotrigine polytherapy	Number OR ORadjusted	2 1.21 [0.14-4.78] 1.00 [0.14-3.60]	3 1.51 [0.29-4.86] 1.34 [0.29-3.95]	0 0.00 [0.00-6.96] -	1 1.41 [0.03-8.53] 1.02 [0.03-5.61]

Odds adjusted: adjusted for maternal age.

Mult. = multiply malformed

Table 5: Distribution* of malformation subgroups by lamotrigine exposure

	Non-AED exposed		Lamotrigine exposed			
Non-chromosomal anomaly subgroup	85,068 registrations**		72 mono or polytherapy exposed registrations		40 monotherapy exposed registrations	
	number	proportion %	number	proportion %	number	proportion %
Nervous system	7,948	9.3	12	16.7	5	12.5
Neural tube defects	3,582	4.2	6	8.3	2	5.0
Spina bifida	1,930	2.3	6	8.3	2	5.0
Hydrocephaly	1,952	2.3	1	1.4	0	-
Microcephaly	730	0.9	2	2.8	1	2.5
Eye	1,379	1.6	2	2.8	1	2.5
Ear, face & neck	1,119	1.3	3	4.2	1	2.5
Congenital heart disease	26,347	31.0	23	31.9	12	30.0
Common arterial truncus	258	0.3	1	1.4	0	-
Ventricular septal defect	11,872	14.0	8	11.1	2	5.0
Atrial septal defect	8,402	9.9	10	13.9	5	12.5
Atrial ventricular septal defect	639	0.8	2	2.8	1	2.5
Tetralogy of fallot	986	1.2	1	1.4	1	2.5
Pulmonary valve stenosis	1,362	1.6	1	1.4	1	2.5
Respiratory	1,675	2.0	3	4.2	1	2.5
Oro-facial clefts ***	5,467	6.4	5	6.9	2	5.0
Cleft lip	3,524	4.1	3	4.2	1	2.5
Cleft palate	1,943	2.3	2	2.8	1	2.5
Digestive system	5,382	6.3	7	9.7	5	12.5
Oesophageal atresia	899	1.1	2	2.8	1	2.5
Atresia/stenosis small intestine	299	0.3	1	1.4	1	2.5
Ano-rectal	1,073	1.3	2	2.8	2	5.0
Diaphragmatic hernia	761	0.9	2	2.8	1	2.5
Urinary	11,093	13.0	11	15.3	4	10.0
Cystic kidney	2,009	2.4	5	6.9	0	-
Cong. Hydronephrosis	3,806	4.5	1	1.4	1	2.5
Genital	6,916	8.1	5	6.9	3	7.5
Hypospadias	5,408	6.4	4	5.6	2	5.0
Limb	16,407	19.3	19	26.4	11	27.5
Limb reduction	2,202	2.6	1	1.4	0	-
Upper limb reduction	1,596	1.9	1	1.4	0	-
Club foot	3,733	4.4	7	9.7	5	12.5
Hip dislocation	2,941	3.5	1	1.4	0	-
Polydactyly	3,568	4.2	5	6.9	2	5.0
Syndactyly	2,181	2.6	1	1.4	0	-
Musculo-skeletal	3,052	3.6	4	5.6	3	7.5
Disorders of skin	1,490	1.8	3	4.2	1	2.5

* *One baby can be counted in more than one subgroup if he/she has multiple malformations, but only once in the total.*

** *the total number of registrations (85,563) minus those exposed to AEDs (495)*

*** *secondary clefts excluded (of whom none were exposed to lamotrigine), see Methods.*

among livebirths, 8.6 per 1,000 among fetal deaths, and 8.3 per 1,000 among terminations.

Table 4 shows the odds ratios for orofacial cleft (in four categories) with antiepileptic drug mono and polytherapy, and lamotrigine mono and polytherapy versus no antiepileptic drug exposure. Adjusting for registry did not materially affect the odds ratios (data not shown); however, adjusting for maternal age did reduce the odds ratios for lamotrigine mono and polytherapy as younger mothers were more likely to take lamotrigine and they were also at a slightly increased risk of orofacial clefts. Therefore for consistency all crude odds ratios and maternal age-adjusted odds ratios are presented. There was no evidence of an increased risk of isolated orofacial cleft relative to other malformations with lamotrigine monotherapy versus no antiepileptic drug exposure (table 4, odds ratio=0.80, 95% CI 0.11–2.85). Nor was there an increased risk for any of the other three categories of orofacial cleft (table 4).

Significantly increased odds ratios were found with any antiepileptic drug exposure versus no antiepileptic drug exposure for orofacial cleft (adjOR=1.43, 95%CI 1.03–1.93), cleft palate (adjOR=2.37, 95%CI 1.54–3.43), and isolated cleft palate (adjOR=1.86, 95% CI 1.07–2.94) (table 4). Odds ratios for any antiepileptic drug therapy were higher for mono than for polytherapy, higher for cleft palate than all orofacial clefts, and higher for isolated and multiple orofacial clefts combined than isolated orofacial clefts alone (table 4). However, due to the small sample sizes, none of these differences were significant.

Table 5 gives the distribution of nonchromosomal malformation subgroups among the 72 lamotrigine exposed and 40 lamotrigine monotherapy exposed cases and controls, compared to non-antiepileptic drug exposed. Shown in table 5 are all EUROCAT subgroups with at least one lamotrigine exposed registration. Cardiac anomalies are the most frequent anomalies, irrespective of exposure (31.0% of non-antiepileptic drug exposed registrations and 31.9% of exposed registrations). Most subgroups had only one or two registrations associated with lamotrigine exposure, so a comparison of proportions with non-antiepileptic drug exposed registrations is imprecise. Moreover, with 37 subgroups, approximately two would be expected by chance alone to show a difference with a probability of less than 1 in 20. In this context, we found one significant observation related to lamotrigine monotherapy: 5 cases of clubfoot (without spina bifida) where 1.7 would be expected ($p<0.05$). In the lamotrigine group including mono and polytherapy three significant differences were found: spina bifida was in excess ($p<0.01$) as well as cystic kidney ($p<0.05$) and clubfoot ($p<0.05$).

The proportion of chromosomal registrations (n=11,781) among all non-antiepileptic drug exposed registrations (chromosomal+nonchromosomal) was 12.0% compared with 4.0% for all lamotrigine exposed (n=3), and 4.8%

for lamotrigine monotherapy (n=2). The relative odds of a nonchromosomal case rather than a chromosomal case given lamotrigine monotherapy was 2.86 (95% CI 1.00–12.5), adjusted for maternal age.

Discussion

We found no evidence of an increased risk of isolated orofacial cleft relative to other nonchromosomal malformations for lamotrigine monotherapy exposure (adjOR=0.80, 95% CI 0.11–2.85), nor any evidence of an increased risk for isolated cleft palate (adjOR=1.01, 95% CI 0.03–5.57). Despite the huge size of our study population, lamotrigine exposure and orofacial clefts are both so rare that the CIs around our estimates of risk are wide. We can at present consider very unlikely a more than threefold risk of isolated orofacial clefts relative to other nonchromosomal malformations. Our results therefore do not support the results of the North American antiepileptic drug Pregnancy Register suggesting a 14-fold increased risk of isolated orofacial clefts against a 1.4-fold increase in non-orofacial cleft malformations, i.e., a 10-fold increased risk of isolated orofacial clefts relative to other malformations [1,2 revised in 6]. We find a twofold higher rate of isolated orofacial clefts in Europe (1.2 per 1,000 births), with some variation between countries, than in the single hospital comparison population used by the North American antiepileptic drug Pregnancy Registry (0.37 per 1,000 revised to 0.6 per 1,000), demonstrating the importance of analyzing comparable exposed and unexposed populations [1,6,14-15]. Given the concern about very high relative risks of orofacial clefts with lamotrigine monotherapy, we report here the results to date, but continued surveillance will allow us to address the possibility of less than threefold relative risks more precisely.

Our case-control study is not designed to assess whether there is a generalized increased risk of malformations with lamotrigine exposure, for which we would need to collect information on non-malformed controls as a comparison group, an area EUROCAT intends to develop in the future. It is possible therefore that some malformations resulting from lamotrigine exposure were in our control group, and moreover that orofacial cleft risk, while not raised relative to other malformations, is raised to the same degree as malformations in general. Our exploratory analyses showed that 1) there is no malformation subgroup that stands out as of particular concern in relation to monotherapy, suggesting that any excess risk, if present, is very non-specific, and 2) nonchromosomal anomalies are overrepresented among lamotrigine-exposed registrations compared to chromosomal, compatible with a generally raised risk of nonchromosomal malformations but based on very small numbers. The evidence from other studies about general malformation risk is inconclusive. To date, publications have reported 2,665 monotherapy exposed pregnancy outcomes, although some of these may come from overlapping pregnancy registers [1,4,6,7,16]. The UK register with 647 lamotrigine monotherapy

exposed fetuses found a general malformation rate of 3.2% (95% CI 2.1–4.9) excluding genetic syndromes. The rate of major malformations among the carbamazepine exposed, the main available comparison group, was 2.2% (95% CI 1.4–3.4) [4]. The GSK International Lamotrigine pregnancy register with 1,053 first trimester lamotrigine exposed fetuses found a prevalence of major congenital anomalies of 2.6% (95% CI 1.7–3.8%) excluding genetic syndromes, without a direct comparison group, and possibly biased by a high 26.6% loss to follow-up rate [6]. The North American antiepileptic drug Pregnancy Registry has reported 15 infants with major malformations among 564 lamotrigine monotherapy exposed fetuses, a rate of 2.7% (95% CI 1.5–4.3), which they compare to an unexposed comparison group rate of 1.6%, giving a relative risk of 1.7 (95% CI 1.0–2.7), or 1.4 excluding orofacial cleft [1]. The Australian Pregnancy register reported 6 malformed babies among 102 lamotrigine monotherapies (5.9%), similar to the rate for carbamazepine (10/198 or 5.0%) [16]. The Swedish Medical Birth Registry reported 14 malformed children, including minor malformations but not including terminations of pregnancy for fetal anomaly, among 347 women using lamotrigine monotherapy, a rate of 4.0% (95% CI 2.3–6.8), compared to a malformation rate of 3.6% in the general population [6]. In Denmark, one case of VSD with lamotrigine polytherapy was reported among 51 lamotrigine exposed fetuses (proportion monotherapy not specified) [7].

We did not have information on lamotrigine dose. We cannot therefore exclude the possibility of a specific risk of orofacial clefts associated with high dosage lamotrigine therapy, although if high dosage therapy were common this would have been detectable in the overall result. A higher mean dose among malformed compared to non-malformed outcomes has been found in the United Kingdom and Australia, although the latter was not significant, but the GSK International Lamotrigine Registry could not find evidence of a dose-response effect [3-4,16]. It is possible that lamotrigine dosages have been increasing in response to findings regarding kinetics during pregnancy, and further surveillance of this issue is necessary [17].

We found an increased risk of orofacial cleft relative to other nonchromosomal malformations for antiepileptic drug exposure in general, which is consistent with much of the literature on drugs such as valproic acid and carbamazepine commonly used by epileptic mothers in our study population [4,18-20]. It is of interest that the increase in risk of cleft palate with antiepileptic drug exposure is higher than that of cleft lip (though not significantly). In our European population, there was a 2.5-fold increase of cleft palate (isolated and multiple combined) relative to other malformations with antiepileptic drug monotherapy. The increase in risk for multiple malformations including orofacial cleft is higher than the increase in risk for isolated orofacial cleft (though again not significantly). We suggest that in the future, attention should not be focused only on isolated orofacial

clefts, but also on multiply malformed individuals with orofacial clefts. The tendency for strong teratogens to produce multiple malformations is well established [21]. We also find higher risks of orofacial clefts with monotherapy than with polytherapy. This may in part reflect the increased risk of other malformations than orofacial cleft rather than the decreased risk of orofacial cleft, with polytherapy.

The main strengths of our study were its huge geographically defined study population, and the well validated, comparable, and specific information about congenital anomaly diagnoses in exposed and unexposed pregnancies. The overall rate of antiepileptic drug exposure—5.8 per 1,000 registrations—is higher than estimated in the general pregnant population (for example, Dutch first trimester antiepileptic drug exposure is 2.5 per 1,000), consistent with a higher risk of malformation with antiepileptic drug exposure, and confirms good ascertainment of antiepileptic drug exposure [22]. The validity of our data for the detection of antiepileptic drug-associated risks of specific malformations is further supported by finding the well known strong association between valproic acid and spina bifida in an embedded validation study (appendix 2), and the commonly documented association of orofacial cleft with other antiepileptic drug.

Post marketing surveillance of the teratogenic effects of antiepileptic drug exposure is essential to provide women and clinicians with the safety information they need to make optimal decisions. Very large population sizes are needed for surveillance as both antiepileptic drug exposure and congenital anomalies are rare. We have demonstrated here the usefulness of a multicentric case-control approach based on congenital anomaly registers for addressing signals relating to specific malformations emanating from pregnancy cohorts.

Our study does not support the very large specific risk of orofacial clefts reported by one previous study (see Note Added in Proof). Further surveillance is recommended to rule out smaller relative risks (less than threefold) of orofacial clefts, to investigate whether other malformation groups are at excess risk, and to investigate risks associated with high dose exposure.

Note added in proof: The full publication of the North American antiepileptic drug Registry study was online April 30, 2008, after acceptance of our paper for publication. The final figures in this publication differ from those we quoted from previous publications; the rate of isolated orofacial clefts among lamotrigine monotherapy-exposed pregnancies was revised to 7.3/1,000, and the rate in the comparison group to 0.7/1,000, resulting in an increased risk of 10.4 (95% CI 4.3–24.9) [1-2,6,23].

Acknowledgment
The authors thank Jim Morrow for early discussions and critical comments on the final paper and the following for their roles in designing and carrying out data collection: Prof. Lorentz Irgens and Jon Gunnar Tufta, Norway; Visnja Tokic, Zagreb, Croatia; Myriam Mols, Hainaut-Namur, Belgium; Monique Devolz, Vaud, Switzerland; Guy Thys, Marie-Paule Mommaert, Catherine van Turnhout, Antwerp, Belgium; Dr. Amanda Neville, IMER Registry, Italy; Erwan Cadio, statistician of the Paris registry, France; Dorit Gotz, Saxony-Anhalt, Germany; Dr. Béatrice Dott, Alsace and the "Institut de Veille Sanitaire–France"; Christine O'Driscoll (Health Service Executive), Ireland;Magdalena Badura-Stronka,Wielkopolska and Poland registries, Poland; Awi Wiesel (Johannes Gutenberg Universitat, Genurtenregister Mainzer Model), Germany; Fabrizio Bianchi (Istituto di Fisiologia Clinica del Consiglio Nazionale delle Ricerche), Italy.

Appendix 1
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Appendix 2

A validation study was also conducted to determine whether the well-known association between valproic acid and spina bifida could be detected in the EUROCAT data, since this was our first full antiepileptic drug study [24]. The same dataset was used, with the same exclusions as described for Part I, but the exposure of interest was valproic acid monotherapy versus no antiepileptic drug use and cases were nonchromosomal spina bifida registrations, controls were non–spina bifida, nonchromosomal registrations. There were 1,979 nonchromosomal spina bifida registrations, of which 23 were valproic acid monotherapy exposed and 1,933 were not exposed to any antiepileptic drug. Of 83,801 non–spina bifida, nonchromosomal registrations, 158 were valproic acid monotherapy exposed and 83,643 were not exposed to any antiepileptic drug. Comparing VPA exposure to no antiepileptic drug exposure, the crude odds ratio was 6.3 (95% CI 4.1–9.8). Adjusting for age made no material difference.

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4 VALPROIC ACID MONOTHERAPY IN PREGNANCY AND MAJOR CONGENITAL MALFORMATIONS

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N Engl J Med 2010;362:2185-2193

Background: The use of valproic acid in the first trimester of pregnancy is associated with an increased risk of spina bifida, but data on the risks of other congenital malformations are limited.

Methods: We first combined data from eight published cohort studies (1565 pregnancies in which the women were exposed to valproic acid, among which 118 major malformations were observed) and identified 14 malformations that were significantly more common among the offspring of women who had received valproic acid during the first trimester. We then assessed the associations between use of valproic acid during the first trimester and these 14 malformations by performing a case–control study with the use of the European Surveillance of Congenital Anomalies (EUROCAT) antiepileptic-study database, which is derived from population-based congenital-anomaly registries. Registrations (i.e., pregnancy outcomes with malformations included in EUROCAT) with any of these 14 malformations were compared with two control groups, one consisting of infants with malformations not previously linked to valproic acid use (control group 1), and one consisting of infants with chromosomal abnormalities (control group 2). The data set included 98,075 live births, stillbirths, or terminations with malformations among 3.8 million births in 14 European countries from 1995 through 2005.

Results: Exposure to valproic acid monotherapy was recorded for a total of 180 registrations, with 122 registrations in the case group, 45 in control group 1, and 13 in control group 2. As compared with no use of an antiepileptic drug during the first trimester (control group 1), use of valproic acid monotherapy was associated with significantly increased risks for 6 of the 14 malformations under consideration; the adjusted odds ratios were as follows: spina bifida, 12.7 (95% confidence interval [CI], 7.7 to 20.7); atrial septal defect, 2.5 (95% CI, 1.4 to 4.4); cleft palate, 5.2 (95% CI, 2.8 to 9.9); hypospadias, 4.8 (95% CI, 2.9 to 8.1); polydactyly, 2.2 (95% CI, 1.0 to 4.5); and craniosynostosis, 6.8 (95% CI, 1.8 to 18.8). Results for exposure to valproic acid were similar to results for exposure to other antiepileptic drugs.

Conclusions: The use of valproic acid monotherapy in the first trimester was associated with significantly increased risks of several congenital malformations, as compared with no use of antiepileptic drugs or with use of other antiepileptic drugs.

Introduction

Valproic acid, which has been used for the treatment of seizure for more than 30 years, has long been recognized as a teratogen. Maternal exposure to valproic acid monotherapy during the first trimester was first linked to an increased risk of congenital spina bifida in the 1980s; subsequent studies confirmed this increased risk and also suggested increased risks of other major congenital malformations [1-8]. Recently, the American Academy of Neurology recommended avoidance of valproic acid during pregnancy if possible [9]. However, if treatment with valproic acid has been providing good seizure control, it can be difficult to change the drug before or during pregnancy [10-11].

Although a number of cohort studies of women exposed to valproic acid in pregnancy have shown an association with a range of malformations, these studies have had limited power individually to detect excess risks of specific malformations. For rare outcomes, such as these specific malformations, large population-based case-control studies are more appropriate [12-18].

We combined the data from cohort studies to identify indications that malformations were occurring at greater frequency than expected among offspring exposed to valproic acid during the first trimester of pregnancy. We then conducted a population-based, case–control study to test our hypotheses, using the antiepileptic-study database established by European Surveillance of Congenital Anomalies (EUROCAT).

Methods

EUROCAT Database

We used the EUROCAT antiepileptic-study database, which included data on affected live births, stillbirths, fetal deaths after 20 or more weeks of gestation, and terminations of pregnancy after prenatal diagnosis for the years 1995 through 2005 from 19 population-based EUROCAT registries in 14 countries (for more information, see Section 1 of the Supplementary Appendix, available with the full text of this article at NEJM .org) [19]. The study sample consisted of 3,881,592 live births and stillbirths, of which 98,075 involved a major congenital malformation.

The standard data recorded for each registration are described in EUROCAT Guide 1.3 [20]. Multiple sources are used to ascertain pregnancy outcomes with malformations (registrations) [21]. Data are managed in a standard

software program that is used by all registries and includes error checks [20]. Infants or fetuses having only malformations categorized as minor according to EUROCAT definitions were excluded [20]. One syndrome and up to eight malformations are coded with International Classification of Diseases, Ninth Revision (ICD-9) or International Classification of Diseases, Tenth Revision (ICD-10) codes, with British Pediatric Association (BPA) one-digit extensions. These codes are regrouped into the standard EUROCAT malformation subgroups [20]. Maternal illness before and during pregnancy (ICD-9 or ICD-10 code plus descriptive information) and drug exposure in the first trimester of pregnancy (descriptive information or Anatomical Therapeutic Chemical [ATC] code) are recorded [22]. The first trimester is defined as the period from the first day of the last menstrual period through the 12th week of gestation.

Ascertainment of Exposure

Information on maternal antiepileptic-drug exposure is mainly obtained from medical hospital records generated during pregnancy (for all 19 registries). Five registries also use other prospectively recorded sources of information (records from general practitioners, pharmacy records, and medical records held by the patient), and three registries use a structured interview or questionnaire after birth to acquire additional information on drug exposure. The persons who recorded information in registries were not aware of the specific hypothesis of the study. Antiepileptic drugs are available by prescription only and are typically supplied for long-term use; thus, medical records were considered to be a good source of data for ascertainment of exposure.

To be included in the EUROCAT antiepileptic study database, a registry must have recorded a diagnosis of maternal epilepsy or antiepileptic drug exposure for at least 3 registrations per 1000 (to exclude registries with low rates of exposure ascertainment) and must have recorded a complete drug name or ATC code for at least 80% of all pregnancies exposed to antiepileptic drugs throughout the study period (to exclude registries with incomplete data on exposure to antiepileptic drugs).

Study Design

We searched PubMed, Web of Science, and Embase for studies addressing exposure to valproic acid in pregnancy. Eight cohort studies met the inclusion criteria and were included in the review (see Sect ion 2 in the Supplementary Appendix for a description of the inclusion criteria) [12-17,23-24]. These eight studies included 1565 pregnancy outcomes in which there was exposure to valproic acid monotherapy during the first trimester; in 118 of these outcomes there was a major congenital malformation as defined by EUROCAT. The overall rate of major congenital malformations was 7.5% (95% confidence interval [CI], 6.3 to 9.0) (Table 1).

Table 1: Overview of included studies [12-17, 23, 24]

			VPA mono exposed		
Study	Country	Included years	number	malformed	Rate (CI 95%)
Samrén 1997	Germany: Berlin & Magdeburg, Finland: Helsinki, Netherlands: Rotterdam & epilepsy institutes	1972-1990	184	16	8.7% (5.4-13.7)
Kaaja 2003	Finland, Helsinki	01/1980-09/1998	61	4	6.6% (2.6-15.7)
Sabers 2004	Denmark, 6 hospitals	09/1996-05/2000	30	2	6.7% (1.9-21.3)
Vajda 2004	Australia, pregnancy registry	07/1999-10/2002	89	15	16.9% (10.5-26.0)
Wide 2004	Sweden	07/1995-12/2001	268	26	9.7% (6.7-13.8)
Wyszinsky 2005	US: Brigham& Boston	02/1997-11/2003	149	16	10.7% (6.3-16.8)
Meador 2006	25 epilepsy centres UK & US	10/1999-02/2004	69	12	17.4% (10.2-28.0)
Morrow 2006	UK, pregnancy registry	12/1996-03/2005	715	44	6.2% (4.6-8.2)
	All studies	1972-2005	1565	135	8.6% (7.3-10.1)
	All studies, according to the EUROCAT MCM classification*		1565	118	7.5% (6.3-9.0)

** According to the EUROCAT major congenital malformation classification (based on ICD-10) 17 were only minor and therefore excluded.*

Al l 14 malformations with prevalences that were significantly higher in the studies of maternal exposure to valproic acid than in the EUROCAT reference group (of 3.8 million) (P<0.05) were included in the case-control study. The number of cases with each of these 14 malformations is detailed in Section 2 in the Supplementary Appendix.

To minimize the chances that we missed a group that warranted inclusion by looking only at cohort studies in the literature review, we also searched case-control studies. The one additional group we found — limb-reduction malformations [25-26] — was excluded to avoid a possible underestimation in the case-control analyses; we examined the group with limb-reduction malformations separately.

We used the EUROCAT antiepileptic-study database to compare the odds of exposure to valproic acid monotherapy among cases (for each of the 14 malformations identified from the literature review) with the odds of exposure in two groups of controls — a group with major malformations other than those under study and a group with malformations associated

with chromosomal abnormalities. Exposure to valproic acid monotherapy during the first trimester was compared with the absence of exposure to antiepileptic drugs and with exposure to an antiepileptic-drug monotherapy other than valproic acid.

Cases were defined as all live births, fetal deaths after at least 20 weeks of gestation, and terminations of pregnancy after prenatal diagnosis with at least one of the following malformations: spina bifida, microcephaly, ventricular septal defect, atrial septal defect, tetralogy of Fallot, pulmonary-valve atresia, hypoplastic right heart, cleft palate (without associated cleft lip), diaphragmatic hernia, gastroschisis, hypospadias, clubfoot, polydactyly, and craniosynostosis. All cases with a diagnosed chromosomal or monogenic syndrome were excluded.

Control group 1 included livebirths, fetal deaths after 20 weeks or more of gestation, and pregnancy terminations after prenatal diagnosis that involved major malformations other than the 14 malformations under study. We excluded chromosomal disorders (the disorders in control group 2), as well as identified syndromes (1806 registrations); cleft lip, cleft lip and palate, or the Pierre Robin sequence without a reported cleft palate (3382); limb-reduction defects (1704); and anencephaly or encephalocele (1759). We also excluded five controls for which type of birth was unknown. Control group 2 comprised live births, fetal deaths after 20 weeks or more of gestation, and pregnancy terminations after prenatal diagnosis that involved malformations associated with chromosomal abnormalities. We excluded two of the entries in this group because type of birth was unknown.

All registrations with recorded maternal antiepileptic-drug use or maternal epilepsy were selected, verified by the registry, and coded according to the name of the antiepileptic drug. After verification, 99.9% of the antiepileptic drugs to which mothers were exposed in the first trimester of pregnancy had been identified. To minimize the risk of misclassification, we excluded all registrations for which there had been a previous diagnosis of maternal epilepsy but for which there was no history of maternal antiepileptic-drug use in the first trimester (a total of 96 cases, 122 controls in group 1, and 19 controls in group 2).

Statistical Analysis

Logistic-regression analysis was used to calculate odds ratios with Stata software, version 10. Crude odds ratios were calculated for all registries, including those without records of valproic acid exposure. Odds ratios were adjusted for maternal age (categorized as less than 25 years, 25 to 29 years, 30 to 34 years, or more than 34 years) and the child's year of birth (categorized as being between 1995 and 1998, between 1999 and 2001, or between 2002 and 2005). Odds ratios were also adjusted for the individual registry

(registries with no entries for valproic acid exposure were excluded) in the comparison of exposure to valproic acid monotherapy with no exposure to antiepileptic drugs; there were too few controls to make this adjustment in other comparisons. For anomalies for which there were fewer than six cases with exposure to valproic acid, no adjustments were made and the exact confidence intervals are presented.

Results

A total of 37,154 cases, 39,472 controls without chromosomal abnormalities (control group 1), and 11,763 controls with chromosomal abnormalities (control group 2) were included in the study. The frequency of maternal use of antiepileptic drugs overall in the first trimester of pregnancy was 5.7 per 1000 registrations, and the frequency of maternal use of valproic acid specifically was 2.0 per 1000. The frequency of exposure to valproic acid was three times as high among cases (3.3 per 1000 registrations) as among controls in both groups (1.1 per 1000) (Table 2).

Table 2: Antiepileptic drug (AED) exposure in the first trimester of pregnancy among registrations (cases and controls)

	Cases* N=37,154		control group 1 N=39,472		control group 2 N=11,763	
	number	Per 1,000 registrations	number	Per 1,000 registrations	number	Per 1,000 registrations
Unexposed to AED	36,869		39,290	-	11725	-
Any AED	285	7.7	182	4.6	38	3.2
Any AED monotherapy	223	6.0	155	3.9	32	2.7
Valproic acid	122	3.3	45	1.1	13	1.1
Other monotherapy	101^	2.7	110^^	2.8	19^^^	1.6

* *All cases with spina bifida, microcephaly, VSD, ASD, tetralogy of Fallot, pulmonary valve atresia, hypoplastic right heart, cleft palate, diaphragmatic hernia, gastroschisis, hypospadias, club foot, polydactyly, or craniosynostosis.*

^ *58 carbamazepine, 21 lamotrigine, 8 phenobarbital, 4 oxcarbazepine, 3 clonazepam, 2 phenytoin, 1 methylphenobarbital, 1 topiramate and 3 unspecified*

^^ *65 carbamazepine, 18 lamotrigine, 9 phenobarbital, 7 oxcarbazepine, 3 phenytoin, 3 primidon, 2 clonazepam, 1 ethosuximide, 1 methylphenobarbital and 1 topiramate*

^^^ *10 carbamazepine, 4 phenobarbital, 2 lamotrigine, 1 clonazepam, 1 oxcarbazepine and 1 phenytoin*

Table 3: Odds ratios (OR) for valproic acid (VPA) monotherapy exposure compared to no antiepileptic drug (AED) exposure and other AED monotherapy exposure, using two malformed control groups

		VPA monotherapy			
malformation sub group**		exposed		ORadj [95%CI]# vs. no AED	ORadj [95%CI]# Vs. other mono
nervous	spina bifida N=2,046	27	C1~	12.7 [7.7-20.7]	5.7 [2.6-12.3]+
			C2~	16.3 [8.0-33.4]	3.5 [1.2-10.0]+
	microcephaly* N=696	2	C1	2.5 [0.3-9.7]^	1.6 [0.1-14.7]^
			C2	2.6 [0.3-11.6]^	1.0 [0.1-9.8]^
congenital heart disease	VSD N=11,711	19	C1	1.6 [0.9-2.7]	2.2 [1.1-4.4]+
			C2	1.8 [0.8-3.9]	1.5 [0.6-4.2]+
	ASD N=8,267	19	C1	2.5 [1.4-4.4]	3.2 [1.5-7.0]+
			C2	3.3 [1.4-7.4]	2.4 [0.8-7.0]+
	tetralogy of Fallot N=960	3	C1	2.8 [0.6-8.6]^	1.5 [0.2-7.9]^
			C2	2.8 [0.5-10.4]^	0.9 [0.1-5.5]^
	pulmonary valve atresia N=311	1	C1	2.8 [0.1-16.7]^	2.4 [0.0-193.6]^
			C2	2.9 [0.1-19.5]^	1.5 [0.0-120.7]^
	hypoplastic right heart N=85	0	C1	-	-
			C2	-	-
cleft palate N=2,244		13	C1	5.2 [2.8-9.9]	3.0 [1.2-7.4]+
			C2	5.2 [2.2-12.3]	1.9 [0.6-5.9]+
diaphragmatic hernia N=754		2	C1	2.3 [0.3-9.0]^	1.2 [0.1-8.9]^
			C2	2.4 [0.3-10.7]^	0.7 [0.1-6.1]^
gastroschisis N=798		1	C1	1.1 [0.0-6.5]^	1.2 [0.0-24.0]^
			C2	1.1 [0.0-7.6]^	0.7 [0.0-15.6]^
hypospadias, boys only N=5,395		32	C1	4.8 [2.9-8.1]	6.7 [2.9-15.2]+
			C2	6.3 [2.6-15.2]	4.1 [1.1-15.0]+
limb	club foot* N=3,676	6	C1	1.6 [0.7-3.7]	1.3 [0.5-3.9]+
			C2	2.2 [0.8-6.7]	1.2 [0.3-4.7]+
	Polydactyly N=3,500	9	C1	2.2 [1.0-4.5]	7.1 [1.8-28.4]+
			C2	2.4 [0.9-6.4]	4.4 [0.8-22.6]+
craniosynostosis N=520		4	C1	6.8 [1.8-18.8]^	4.9 [0.7-55.2]^
			C2	7.0 [1.7-22.9]^	2.9 [0.4-35.8]^

** *one case/control can be counted in more than one subgroup.*

* *club foot and microcephaly without spina bifida*

\# *OR are adjusted for reporting registry, birth year and maternal age*

~ *C1 control group 1: registrations without chromosomal abnormalities. C2 control group 2: registrations with chromosomal abnormalities (numbers are presented in table 2).*

\+ *OR adjusted for birth year and maternal age*

^ *OR not adjusted due to small number of exposed cases*

The number of unexposed cases can be found in web appendix 3

In analyses of cases and the controls in group 1, exposure to valproic acid monotherapy during the first trimester as compared with no exposure to antiepileptic drugs during that period was associated with significant increases in the risks of spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly, and craniosynostosis but not in the risks of microcephaly, tetralogy of Fallot, pulmonary-valve atresia, diaphragmatic hernia, ventricular septal defect, hypoplastic right heart (no exposed cases), gastroschisis, or club foot (Table 3). Adjustment for reporting registry, birth year of the registration, and maternal age did not substantively affect the results (see Section 3 in the Supplementary Appendix for details).

Using the same control group, we found generally similar associations between valproic acid exposure and malformations when valproic acid monotherapy was compared with monotherapy with another antiepileptic drug — with two exceptions. When compared with use of another antiepileptic drug, valproic acid use was not associated with a significantly increased risk of craniosynostosis but was associated with a significantly increased risk of ventricular septal defect.

In corresponding analyses comparing cases with the controls in group 2 (those with chromosomal abnormalities), the results were generally similar. Separate analyses of the suggested association between valproic acid exposure and limb reduction showed a significantly increased risk of limb reduction (crude odds ratio, 3.4; 95% CI, 1.6 to 7.2) as compared with the absence of exposure to antiepileptic drugs.

In control group 1, we also compared the distribution of malformations among controls exposed to valproic acid with the distribution among controls without exposure to antiepileptic drugs and found no significant differences (data not shown). We found no malformations other than those reported in the literature that had a significant association with valproic acid exposure in this group.

Discussion

In a review of published cohort studies, we identified 14 major congenital malformations for which the risk appeared to be significantly increased in association with exposure to valproic acid monotherapy during the first trimester of pregnancy as compared with no exposure to antiepileptic drugs during the first trimester. We then tested these indications in a large population-based case-control study and found significant associations between exposure to valproic acid monotherapy in the first trimester (as compared with no exposure to antiepileptic drugs) and six of these conditions: spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly, and craniosynostosis. Risks for five of these conditions were 2 to 7 times as high for exposed fetuses, and the risk for the sixth condition, spina bifida, was 12 or 16 times as high, depending on the control group used. We also found an

association between limb defects and exposure to valproic acid monotherapy as compared with no exposure to antiepileptic drugs, as suggested in previous case-control studies.

Significant associations with valproic acid exposure were noted for five of the six specific malformations in analyses comparing exposure to valproic acid monotherapy with other antiepileptic-drug monotherapy; an association with craniosynostosis was not found. A significant association with ventricular septal defect was detected, but only for the comparison of cases with controls in the group that had malformations not associated with a chromosomal abnormality — not for the comparison of cases with the other control group. Although the observational nature of this study precludes a conclusion about cause and effect, these findings support a relationship of these malformations to valproic acid specifically rather than to antiepileptic drugs generally or to underlying epilepsy. Valproic acid is used for various indications in European countries, which means that its use is unlikely to be very strongly related to a particular type or severity of epilepsy. However, we do not have information on the type or severity of epilepsy and therefore cannot rule out the possibility of confounding by indication.

Studies evaluating the risk of general malformations after in utero exposure to an antiepileptic drug as compared with no such exposure have shown that the risk is significantly higher with exposure to valproic acid than with exposure to other antiepileptic drugs. Furthermore, these studies have suggested increased risks of malformations in general in association with higher doses of valproic acid as compared with lower doses [13,15-17]. Since our data set does not include dose information, we were not able to address this question.

Previous studies of valproic acid monotherapy during the first trimester and the risk of specific malformations, other than spina bifida, have generally been limited by relatively small samples or potential selection bias, since they have not been population-based [11,13,15,17,27-28]. Our results are in line with those of another large, population-based, case-control registry study of congenital malformations in which the control group had malformations; specific associations were reported between valproic acid exposure and spina bifida, hypospadias, malformations of the brain and heart, and limb-reduction malformations [26].

A recent study showed that children exposed to valproic acid in utero were more likely to have impaired cognitive function at 3 years of age than children exposed in utero to other antiepileptic drugs [29]. The American Academy of Neurology has recommended avoiding valproic acid in pregnancy, if possible, on the basis of evidence that exposure to valproic acid is associated with an increased risk of major congenital malformations and poor cognitive outcomes and confers a higher risk than that associated with exposure to other antiepileptic drugs [9].

For malformations seen less frequently, our study was able to rule out very large risks but not smaller risks. The confidence limits were wide, showing that even a study of nearly 4 million pregnancies is not enough to address a potentially moderate association between rare malformations and relatively rare drug exposures.

A limitation of our study, as discussed above, is the lack of information on potential confounders. Furthermore, we used controls with malformations instead of those without malformations, since EUROCAT does not include detailed population-based data on pregnancy outcomes without malformations. An advantage of using controls with malformations is that it minimizes the potential for recall bias and other possible sources of differential exposure ascertainment, although such biases would be unlikely to influence the results, since most drug information was recorded before the outcome of pregnancy was known. Use of controls with malformations for comparison could lead to a conservative estimation of the risk associated with valproic acid exposure if some of the malformations present in the control group were also associated with this exposure; however, by design we excluded from the control groups malformations previously associated with valproic acid exposure. The rate of valproic acid exposure was similar in the two control groups (1.1 per 1000), and the point estimates for the control group with chromosomal abnormalities were similar but slightly higher than those for the control group without chromosomal abnormalities in comparisons of exposure to an antiepileptic drug with no such exposure. We therefore concluded that there was likely to be little or no contamination of our control groups with malformation types associated with valproic acid exposure and that underestimation of odds ratios because of this bias was unlikely.

Although the relative risks of several malformations were increased in association with exposure to valproic acid during the first trimester, it should be recognized that the absolute rates of specific malformations are low, and the majority of children born to mothers who take valproic acid do not have malformations. For example, the baseline prevalence of spina bifida is about 0.5 cases per 1000 (see Section 2 in the Supplementary Appendix). We calculated an adjusted odds ratio of 12.7 for the risk of spina bifida when comparing exposure to valproic acid with no exposure to an antiepileptic drug (Table 3); the absolute risk of having a child with spina bifida is approximately 0.6% in cases of exposure to valproic acid monotherapy during the first trimester. The estimated absolute risks for the other five malformations after exposure are as follows: atrial septal defect, 0.5%; cleft palate, 0.3%; hypospadias, 0.7%; polydactyly, 0.2%; and craniosynostosis, 0.1%. In determining whether to prescribe antiepileptic drugs, as well as which drug to prescribe, several factors must be taken into account, among them the goal of optimizing seizure control in the individual patient. The decision should be

made by the patient and her clinician after consideration of the benefits and risks of various agents.

In summary, we found that exposure to valproic acid during the first trimester was associated with increased risks of six specific malformations, as compared with no exposure to antiepileptic drugs, and the risks of five of these six malformations remained significantly increased when we compared valproic acid exposure with exposure to other antiepileptic drugs. Our findings provide further support for the recommendation of the American Academy of Neurology to avoid the use of valproic acid, if possible, in pregnant women [9]. Since switching drugs during or just before pregnancy is difficult, the risks associated with valproic acid use should be routinely considered in choosing therapy for women with childbearing potential.

Appendix

Members of the EUROCAT Antiepileptic Study Working Group include the following: C. Verellen-Dumoulin (Centre de Génétique Humaine Institut de Pathologie et de Génétique), V. Nelen (Provinciaal Instituut voor Hygiene), Belgium; I. Barisic (Children's University Hospital Zagreb), Croatia; E. Garne (Lillebaelt Hospital, Kolding), Denmark; B. Khoshnood (Institut National de la Santé et de la Recherche Medicale), B. Doray (Registre des Malformations Congenitales d'Alsace), France; S. Poetzsch (Otto-von-Guericke Universität Megdeburg), A. Wiesel (Johannes Gutenberg Universität, Geburtenregister Mainzer Modell), Germany; M. O'Mahony (Health Service Executive), Ireland; A. Pierini (Istituto di Fisiologia Clinica del Consiglio Nazionale delle Ricerche), F. Rivieri (Azienda Ospedaliero Universitaria di Ferrara), Italy; M. Gatt (Department of Health Information and Research), Malta; M. Bakker (University Medical Center Groningen, University of Groningen), the Netherlands; K. Melve (Norwegian Institute of Public Health, Medical Birth Registry of Norway), Norway; A. Latos-Bielenska, J.P. Mejnartowicz (Uniwersytet Medyczny im. Karola Marcinkowskiego w Poznaniu), Poland; I. Portillo (Direccion Salud Publica, Departamento Sanidad, Gobierno Vasco), Spain; M.-C. Addor (Registre Vaudois des Malformations), Switzerland; D. Tucker (Swansea National Health Service Trust, Congenital Anomaly Register and Information Service for Wales), D. Wellesley (Southampton University Hospitals Trust), United Kingdom.

Web Appendix 1

Participating registries: Belgium (Antwerp and Hainaut), Croatia (Zagreb), Denmark (Odense), France (Paris and Strasbourg), Germany (Mainz and Saxony Anhalt), Ireland (Cork & Kerry), Italy (Emilia Romagna and Tuscany), Malta, Netherlands (northern part), Norway, Poland (Wielkopolska, Poland), Spain (Basque Country), Switzerland (Vaud) and UK (Wales)

Web Appendix 2

We searched PubMed, Web of Science and Embase for studies addressing VPA exposure in pregnancy and found over 1500 studies using the following search strategy: {"valproic acid"[Mesh] OR "epilepsy/drug therapy"[Majr] OR "antiepileptic drugs"[ti] OR "AED"[ti]} AND {"congenital abnormalities"[Majr] OR "pregnancy complications/drug therapy"[Majr] OR "birth defects"[ti]}. The criteria for selecting studies were: non-overlapping cohort studies that reported a case list with detailed information about malformations, reported the size of the VPA exposed cohort and reported the definition of the study population and the study period. Eight cohort studies met the criteria (Table 1) [12-17, 23-24]. Authors of two studies that did not include sufficient details to categorize some malformations were contacted to obtain additional information [13,16].

In the 8 studies, malformations reported in offspring with first trimester VPA exposure were classified according to the EUROCAT congenital anomaly subgroups. The EUROCAT AED database was used as the reference group; the prevalences of various malformations in this database were calculated after excluding registrations with maternal AED exposure, maternal epilepsy, or chromosomal anomalies. Differences in prevalence between the published studies and EUROCAT reference group were compared using a chi square test with Yates' correction (Program used: S-PLUS7.0). All malformation subgroups for which the prevalence in studies of maternal VPA exposure was significantly higher than in the EUROCAT referent group (at p-value less than 0.05) were considered to be "signals" and were studied further in the case-control study (see table below).

Result of the review of the 8 cohort studies [12–17, 23, 24]^.

	Literature N=1,565		EUROCAT N=3,869,947		
Malformation sub group	number	prev./1000	number*	prev./1000	p-value#
spina bifida	22	14.1	1933	0.5	p < 0.001
microcephaly	2	1.3	745	0.2	p = 0.030
VSD	12	7.7	11896	3.1	p < 0.001
ASD	11	7.0	8428	2.2	p < 0.001
tetralogy of Fallot	3	1.9	991	0.3	p = 0.001
pulmonary valve atresia	3	1.9	339	0.1	p < 0.001
hypoplastic right heart	1	0.6	99	0.03	p = 0.023
cleft palate	13	8.3	2338	0.6	p < 0.001
diaphragmatic hernia	4	2.6	766	0.2	p < 0.001
Gastroschisis	2	1.3	807	0.2	p = 0.041
Hypospadias	22	14.1	5418	1.4	p < 0.001
club foot	8	5.1	3847	1.0	p < 0.001
Polydactyly	8	5.1	3594	0.9	p < 0.001
craniosynostosis	5	3.2	551	0.1	p < 0.001

^ *All specific malformations found in the literature review were defined over 75 malformation sub groups; 41 sub groups were filled with at least one case and 14 of these sub groups showed a significant increased prevalence compared with the EUROCAT population.*

\# *calculated with a chi square test with Yate's correction*

* *excluding chromosomal and AED exposed registrations*

Web Appendix 3

Unadjusted odds ratio's for VPA monotherapy compared with 'no AED' (first column) and 'other AED monotherapy' (second column) using non-chromosomal controls (C1) and chromosomal controls (C2)

		VPA monotherapy					
malformation sub group		exposed		ORunadj [95%CI]# vs. no AED	ORunadj [95%CI]# vs. other mono	No AED exposed	Other mono exposed
nervous	spina bifida N=2,046	27	C1	11.9 [7.0-19.5]	5.1 [2.3-11.6]	1996	13
			C2	12.2 [6.1-25.8]	3.0 [1.0-8.9]		
	microcephaly* N=696	2	C1	2.5 [0.3-9.7]	1.6 [0.1-14.7]	690	3
			C2	2.6 [0.3-11.6]	1.0 [0.1-9.8]		
congenital heart disease	VSD N=11,711	19	C1	1.4 [0.8-2.5]	2.0 [09-4.3]	11659	23
			C2	1.5 [0.7-3.2]	1.2 [0.4-3.4]		
	ASD N=8,267	19	C1	2.0 [1.1-3.5]	3.1 [1.3-7.1]	8216	15
			C2	2.1 [1.0-4.6]	1.9 [0.6-5.5]		
	tetralogy of Fallot N=960	3	C1	2.8 [0.6-8.6]	1.5 [0.2-7.9]	951	5
			C2	2.8 [0.5-10.4]	0.9 [0.1-5.5]		
	pulmonary valve atresia N=311	1	C1	2.8 [0.1-16.7]	2.4 [0.0-193.6]	309	1
			C2	2.9 [0.1-19.5]	1.5 [0.0120.7]		
	hypoplastic right heart N=85	0	C1	-	-	84	1
			C2	-	-		
cleft palate N=2,244		13	C1	5.1 [2.5-9.7]	2.9 [1.1-7.7]	2215	11
			C2	5.3 [2.3-12.4]	1.7 [0.5-5.8]		
diaphragmatic hernia N=754		2	C1	2.3 [0.3-9.0]	1.2 [0.1-8.9]	747	4
			C2	2.4 [0.3-10.7]	0.7 [0.1-6.1]		
gastroschisis N=798		1	C1	1.1 [0.0-6.5]	1.2 [0.0-24.0]	794	2
			C2	1.1 [0.0-7.6]	0.7 [0.0-15.6]		
hypospadias, boys only N=5,395		32	C1	4.5 [2.6-7.8]	6.6 [2.8-16.6]	5343	11
			C2	4.9 [2.1-13.1]	3.3 [0.8-13.4]		
limb	club foot* N=3,676	6	C1	1.4 [0.5-3.4]	1.2 [0.4-3.8]	3651	12
			C2	1.5 [0.5-4.2]	0.7 [0.2-2.8]		
	Polydactyly N=3,500	9	C1	2.3 [1.0-4.7]	5.5 [1.4-25.4]	3481	4
			C2	2.3 [0.9-5.9]	3.3 [0.7-17.4]		
craniosynostosis N=520		4	C1	6.8 [1.8-18.8]	4.9 [0.7-55.2]	513	2
			C2	7.0 [1.7-22.9]	2.9 [0.4-35.8]		

The numbers in the table can not be summed to get the total because polytherapy is not shown (eg. spina bifida 27+1996+13=2036 plus 10 polytherapy exposed=2046)

^ *C1: Control group 1: all non-chromosomal, non-monogenic registrations without any of the malformations under study*
C2: Control group 2: all chromosomal malformations (for exact definitions, see Methods)

* *club foot and microcephaly without spina bifida*

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5 INTRAUTERINE EXPOSURE TO CARBAMAZEPINE AND SPECIFIC CONGENITAL MALFORMATIONS: SYSTEMATIC REVIEW AND CASE-CONTROL STUDY

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BMJ 2010;341:c6581

Objective: To identify specific major congenital malformations associated with use of carbamazepine in the first trimester of pregnancy.

Design: A review of all published cohort studies to identify key indications and a population based case-control study to test these indications.

Setting: Review of PubMed, Web of Science, and Embase for papers about carbamazepine exposure in the first trimester of pregnancy and specific malformations, and the EUROCAT Antiepileptic Study Database, including data from 19 European population-based congenital anomaly registries, 1995-2005.

Participants: The literature review covered eight cohort studies of 2680 pregnancies with carbamazepine monotherapy exposure, and the EUROCAT dataset included 98 075 registrations of malformations covering over 3.8 million births.

Main outcome measures: Overall prevalence for a major congenital malformation after exposure to carbamazepine monotherapy in the first trimester. Odds ratios for malformations with exposure to carbamazepine among cases (five types of malformation identified in the literature review) compared with two groups of controls: other non-chromosomal registrations of malformations and chromosomal syndromes.

Results: The literature review yielded an overall prevalence for a major congenital malformation of 3.3% (95% confidence interval 2.7 to 4.2) after exposure to carbamazepine monotherapy in the first trimester. In 131 registrations of malformations, the fetus had been exposed to carbamazepine monotherapy. Spina bifida was the only specific major congenital malformation significantly associated with exposure to carbamazepine monotherapy (odds ratio 2.6 (95% confidence interval 1.2 to 5.3) compared with no antiepileptic

drug), but the risk was smaller for carbamazepine than for valproic acid (0.2, 0.1 to 0.6). There was no evidence for an association with total anomalous pulmonary venous return (no cases with carbamazepine exposure), cleft lip (with or without palate) (0.2, 0.0 to 1.3), diaphragmatic hernia (0.9, 0.1 to 6.6), or hypospadias (0.7, 0.3 to 1.6) compared with no exposure to antiepileptic drugs. Further exploratory analysis suggested a higher risk of single ventricle and atrio-ventricular septal defect.

Conclusion: Carbamazepine teratogenicity is relatively specific to spina bifida, though the risk is less than with valproic acid. Despite the large dataset, there was not enough power to detect moderate risks for some rare major congenital malformations.

Introduction

Carbamazepine is one of the most commonly used antiepileptic drugs in Europe among women of child-bearing age. Several cohort studies have evaluated the risk of major congenital malformations associated with carbamazepine, and it seemed to be less teratogenic than valproic acid [1-6]. Although around 3000 pregnancies with recorded carbamazepine exposure have been described in the literature, each individual study on its own is too small to have the statistical power to detect risks for specific congenital malformations compared with other antiepileptic drugs [4,7-8].

The EUROCAT (European Surveillance of Congenital Anomalies) Antiepileptic Study Database, which was set up for a study of lamotrigine, covered 3,881,592 births and contains 131 registrations of malformation in pregnancy outcomes exposed to carbamazepine monotherapy, more than in any other published study [9]. This enabled the examination of risks of specific major congenital malformations associated with carbamazepine monotherapy.

We reviewed and combined studies on carbamazepine to identify indications of increased risks of specific malformations after intrauterine exposure to carbamazepine monotherapy in the first trimester of pregnancy. We tested these indications, or prior hypotheses, in a case-control study using two control groups of malformations.

Methods

EUROCAT

The EUROCAT Antiepileptic Study Database has been previously described [6,9-10]. It was drawn from 19 population based registries of congenital anomaly in Europe, covering 3,881,592 births in Europe in 1995-2005 and 98,075 major congenital malformations: 86,291 non-chromosomal and 11,784

chromosomal. Information was available for live births, still births or late fetal deaths from 20 weeks' gestation, and terminations of pregnancy after prenatal diagnosis. The database includes data from registries in Belgium(Antwerp and Hainaut), Croatia (Zagreb), Denmark (Odense), France (Paris and Strasbourg), Germany (Mainz and Saxony-Anhalt), Ireland (Cork and Kerry), Italy (Emilia Romagna and Tuscany), Malta, Netherlands (northern part), Norway, Poland (Wielkopolska, rest of Poland), Spain (Basque Country), Switzerland (Vaud), and the United Kingdom (Wales).

Literature review

We reviewed PubMed, Web of Science, and Embase for papers about carbamazepine exposure in the first trimester of pregnancy and specific malformations using the following search strategy: ((“Carbamazepine”[Mesh] OR “antiepileptic drugs”[ti] OR “AED”[ti]) AND (“Congenital Abnormalities”[Majr] OR “Pregnancy Complications/drug therapy”[Majr] OR “birth defects”[ti]) NOT “Clinical Trials, Phase I as Topic”[Mesh] NOT (“Models, Animal”[Mesh] OR “Animal Experimentation”[Mesh])) AND “Cohort Studies”[Mesh] (PubMed n=44) and ‘carbamazepine and malformation and pregnancy’ (Web of Science n=141 and Embase n=30). We identified nine cohort studies that contained a specified case list of all pregnancy outcomes with malformation (table 1) [1-5,11-14]. We contacted four authors to get more information about the case list; three were able to supply the information requested and were included, the fourth was excluded [1, 3-5].

The eight cohort studies included outcomes of 2,680 pregnancies with carbamazepine monotherapy exposure. Of these, 101 babies had a malformation, 89 of which were classified as major according to EUROCAT and were classified according to 49 standard EUROCAT congenital anomaly subgroups10. A case could be counted only once in each subgroup but could be counted in more than one subgroup. The 12 cases classified as only minor malformations according to the EUROCAT classification were excluded [10]. Based on these eight cohorts, the overall prevalence for a major congenital malformation after exposure to carbamazepine monotherapy in the first trimester was 3.3% (95% confidence interval 2.7 to 4.2) (table 1).

The prevalence for specific subgroups of congenital anomaly was calculated by dividing the subgroup totals by the total outcomes in pregnancies with carbamazepine monotherapy exposure. This prevalence was compared with the prevalence in the population covered by the EUROCAT Antiepileptic Study Database (excluding pregnancies with exposure to antiepileptic drugs), with χ^2 test with Yate's correction in S-PLUS 7.0. In the combined literature cohort five subgroups had a significantly higher prevalence than expected ($P<0.05$) (table 2) and were considered “indications” to be tested in the case-control study: spina bifida, total anomalous pulmonary venous return, cleft lip (with or without palate), diaphragmatic hernia, and hypospadias.

Table 1: Overview of the included cohort studies [2-5,11-14]

			Carbamazepine mono exposed		
Study	Country	Included years	number	malformed	Rate (CI 95%)
Samrén 1997	Germany: Berlin & Magdeburg, Finland: Helsinki, Netherlands: Rotterdam & epilepsy institutes	all between 1972-1990	280	22	7.9% (5.2-11.6)
Diav-Citrin 2001	Israeli Teratogen Information Service	01/1989-03/1999	108	6	5.6% (2.6-11.8)
Kaaja 2003	Finland, Helsinki	01/1980-09/1998	363	10	2.8% (1.5-5.0)
Sabers 2004	Denmark, 6 hospitals	09/1996-05/2000	18	0	0% (0.0-17.6)
Wide 2004	Sweden	07/1995-12/2001	703	28	4.0% (2.8-5.7)
Meador 2006	25 epilepsy centres UK & US	10/1999-02/2004	110	5	4.5% (2.0-10.2)
Morrow 2006	UK, pregnancy registry	12/1996-03/2005	900	20	2.2% (1.4-3.4)
Vajda 2007	Australia, pregnancy registry	07/1999-10/2002	198	10	5.1% (2.8-9.0)
	All studies	1972-2005	2680	101	3.8% (3.1-4.6)
	All studies, according to the EUROCAT MCM classification*		2680	89	3.3% (2.7-4.2)

* *According to the EUROCAT major congenital malformation classification (based on ICD-10) 12 were only minor malformations and therefore excluded.*

Table 2: Result of the review of the 8 cohort studies. All specific malformations found in the literature review were classified to 75 malformation subgroups; 49 subgroups had at least one case and 5 of these subgroups showed a significant increased prevalence compared with the EUROCAT population. These 5 are presented in this table.

	Literature		EUROCAT		
	number N=2680	prev./1000	number* N=3,869,947	prev./1000	p-value#
anomalous pulmonary venous return	2	0.75	134	0.03	p < 0.0000
cleft lip, with or without palate	7	2.61	3634	0.94	p = 0.0121
diaphragmatic hernia	3	1.12	766	0.20	p = 0.0070
hypospadias	12	4.48	5418	1.40	p = 0.0001
spina bifida	6	2.24	1933	0.50	p = 0.0003

\# *Calculated with a chi square test with Yate's correction*

* *excluding chromosomal and antiepileptic drug exposed registrations*

To check if we missed any indication by concentrating on published cohort studies in the literature review, we searched for additional indications in abstracts of case-control studies. We found one additional indication for the risk of cleft palate [15]. We excluded cleft palate malformations from our study control group and examined these registrations separately. Indications from other case-control studies had all been identified in the review of cohort studies.

Case-control study

We carried out a population based case-control study to test the five indications identified in the literature review. We compared the odds of exposure to carbamazepine monotherapy among each of these five malformations under study (cases) with the odds of exposure among two control groups of malformations: a non-chromosomal and a chromosomal control group. As valproic acid has been shown to be more teratogenic than other antiepileptic drugs, we compared carbamazepine monotherapy exposure with "no antiepileptic drug exposure", "valproic acid monotherapy", and "other antiepileptic drug monotherapy" (excluding valproic acid) [6].

Case definition

Cases were defined as all live births, fetal deaths from 20 weeks' gestation, and terminations of pregnancy after prenatal diagnosis, non-chromosomal and non-monogenic, with at least one of the following major congenital malformations: spina bifida, total anomalous pulmonary venous return, cleft lip (with or without palate), diaphragmatic hernia, and hypospadias. We excluded all cases of diagnosed monogenic syndrome (n=180).

Control definition

Control group 1 included livebirths, fetal deaths from 20 weeks' gestation, and terminations of pregnancy after prenatal diagnosis that involved major malformations other than the five malformations under study. We excluded chromosomal syndromes as well as registrations with cleft palate or Pierre Robin sequence (n=2320) and all anencephaly or encephalocele (n=1860) to avoid possible misclassification from an aetiologically similar diagnosis. Five controls were excluded because of unknown type of birth.

Control group 2 included live births, fetal deaths from 20 weeks' gestation, and terminations of pregnancy after prenatal diagnosis with chromosomal syndromes. Two controls in this group were excluded because of unknown type of birth.

Exposure

All registrations with associated maternal use of antiepileptic drugs or maternal epilepsy, or both, were selected, verified by the local registry, and

coded by ATC (Anatomical Therapeutic Chemical Classification) code [16]. After verification over 99% of all drug names were known. In 95% of all registrations with carbamazepine exposure, there was a diagnosis of maternal epilepsy. To avoid misclassification of exposure we excluded all registrations with an associated reported diagnosis of maternal epilepsy but without maternal use of antiepileptic drugs in the first trimester (42 cases: spina bifida (8), cleft lip (12), diaphragmatic hernia (5), and hypospadias (17); and 195 controls). We compared carbamazepine monotherapy in the first trimester of pregnancy with "no antiepileptic drug exposure", "valproic acid monotherapy", and "other antiepileptic drug monotherapy excluding valproic acid". In the comparison with valproic acid monotherapy we excluded from the control group malformations associated with valproic acid exposure: atrial septal defect, polydactyly, and craniosynostosis [6].

Statistical analyses

Odds ratios were calculated with logistic regression in Stata. Crude odds ratios were calculated without correction for any possible confounder and including all registries even if they had no registration with carbamazepine exposure (see appendix 1 on). Odds ratios were adjusted for maternal age (categorized into <25, 25-29, 30-34, and >34 years) and year of birth of the child (categorized as before 1999, 1999-2001, and 2002 onwards). If there were sufficient numbers of cases the adjusted odds ratio was also corrected for the reporting registry (registries with no carbamazepine exposure were excluded). No systematically recorded information on other potentially important confounders was available in our dataset.

We also conducted an exploratory analysis to check if there was evidence in the data of specific malformations related to carbamazepine monotherapy that were not identified by the literature review. We compared the proportion of each subgroup of specific non-chromosomal congenital anomalies (excluding the five case groups, but reincluding cleft palate, anencephaly, and encephalocele) for malformations with carbamazepine monotherapy exposure with all non-chromosomal EUROCAT registrations without reported epilepsy or use of antiepileptic drugs. We compared differences between proportions with a χ^2 test.

Results

In the included study population 516 registered malformations were in pregnancy outcomes with recorded exposure to any antiepileptic drug in the first trimester of pregnancy, 5.5 per 1000 registrations (516/93 436). The exposure to antiepileptic drugs was more than twice as high among the cases (10.9 per 1000 registrations) than among the controls (5.0 and 3.2 per 1000 registrations) (table 3). This difference between cases and controls

Table 3: Antiepileptic drug (AED) exposure among registrations (cases and controls)

	Non chromosomal cases under study* N=11,790		Control group 1# N=69,883		Control group 2^ N=11,763	
	number	Per 1,000 registrations	number	Per 1,000 registrations	number	Per 1,000 registrations
Any AED	129	10.9	349	5.0	38	3.2
Any AED monotherapy	104	8.8	282	4.0	32	2.7
VPA monotherapy	66	5.6	102	1.5	13	1.1
CBZ monotherapy	16	1.4	105	1.5	10	0.9
other monotherapy	22~	1.9	75**	1.1	9^^	0.8

* *All cases with anomalous pulmonary venous return, cleft lip (with or without palate), diaphragmatic hernia, hypospadias or spina bifida.*

\# *non chromosomal malformed registration without any of the malformations under study*

^ *all chromosomals*

~ *9 phenobarbital, 5 lamotrigine, 3 clonazepam, 2 levetriacetam and 3 unspecified antiepileptic drugs.*

** *33 lamotrigine, 15 phenobarbital, 10 oxcarbazepine, 5 phenytoin, 3 clonazepam, 3 primidon, 2 methylphenobarbital, 2 topiramate, 1 ethosuximide and 1 unspecified AED.*

^^ *4 phenobarbital, 2 lamotrigine, 1 clonazepam, 1 oxcarbazepine, 1 phenytoin*

was not seen in registered malformations with any recorded exposure to carbamazepine monotherapy. The exposure to carbamazepine monotherapy was comparable among cases (1.4/1000) and among non-chromosomal controls (1.5/1000). The exposure among chromosomal controls was lower (0.9/1000). The exposure to valproic acid monotherapy was higher among cases than among both control groups (table 3).

The five case subgroups included 11,790 cases (table 4). Eighty two cases were included in two different subgroups. The control groups consisted of 69,883 non-chromosomal malformed registrations and 11,763 chromosomal registrations.

Carbamazepine monotherapy v no antiepileptic drugs

In the comparison of carbamazepine monotherapy exposure with no antiepileptic drugs, one of the five indications found in the literature was confirmed: the odds ratio for spina bifida was 2.6 (95% confidence interval 1.2 to 5.3) compared with non-chromosomal controls and 4.2 (1.5 to 11.2) compared with chromosomal controls. The odds ratios for cleft lip (with or without palate), diaphragmatic hernia, and hypospadias were not appreciably increased; they were all around or below 1, though for diaphragmatic hernia the confidence interval was wide. We could not perform meaningful analyses for total anomalous pulmonary venous return because we did not have any cases with exposure to carbamazepine (table 4).

Table 4: Adjusted odds ratios (OR) for antiepileptic drug (AED) and carbamazepine (CBZ) exposure compared to no antiepileptic drug, valproic acid (VPA) and other antiepileptic drug exposure, using a non-chromosomal malformed control group (C1) and chromosomal control group (C2)

			Carbamazepine monotherapy		
malformation subgroup	exposed		ORadj [95%CI]# vs. no AED	ORadj [95%CI]# vs. VPA mono~	ORadj [95%CI]# vs. other mono^
spina bifida N=2,048	8	C1	2.6 [1.2-5.3]	0.2 [0.1-0.6]+	1.1 [0.4-3.6]+
		C2	4.2 [1.5-11.2]	0.3 [0.1-1.2]+	1.4 [0.3-6.6]+
total anomalous pulm. v. return N=132	0	C1	-	-	-
		C2	-	-	-
cleft lip (with or without palate) N=3,544	1	C1	0.2 [0.0-1.3]	0.3 [0.0-2.6]+	0.1 [0.0-0.6]+
		C2	0.2 [0.0-1.7]	0.2 [0.0-2.7]+	0.0 [0.0-0.5]+
diaphragmatic hernia N=755	1	C1	0.9 [0.1-6.6]	0.5 [0.0-4.5]+	0.2 [0.0-2.2]+
		C2	1.0 [0.1-8.5]	0.4 [0.0-5.8]+	0.2 [0.0-2.5]+
hypospadias, boys only N=5,393	6	C1	0.7 [0.3-1.6]	0.2 [0.1-0.5]+	0.8 [0.2-2.9]+
		C2	0.5 [0.2-1.8]	0.1 [0.0-0.7]+	0.4 [0.1-4.0]+

~ *valproic acid (VPA) exposed malformed excluding malformations associated with valproic acid exposure. Cases exposed to VPA: 27 spina bifida, 2 TAPVR, 3 cleft lip, 2 diaphragmatic hernia, 32 hypospadias.*

^ *other monotherapy, excluding valproic acid. Cases exposed to other AED monotherapy: 5 spina bifida, 0 TAPVR, 10 cleft lip, 3 diaphragmatic hernia, 5 hypospadias.*

\# *OR are adjusted for reporting centre, year of birth, maternal age*

\+ *Ors adjusted for year of birth and maternal age (not centre)*

Carbamazepine monotherapy v other antiepileptic drug monotherapy

In contrast with the comparison with "no antiepileptic drugs" the exposure to carbamazepine monotherapy resulted in a reduced risk for spina bifida compared with valproic acid monotherapy, which was significant in the comparison with control group 1 (0.2, 0.1 to 0.6).

Compared with other antiepileptic drug monotherapy excluding valproic acid, exposure to carbamazepine monotherapy showed no difference in the risk for spina bifida (1.1, 0.4 to 3.6).

For hypospadias we found a significantly lower risk for carbamazepine monotherapy than for valproic acid monotherapy (0.2, 0.1 to 0.5) and again no difference in risk in comparison with other antiepileptic drug monotherapy excluding valproic acid (0.8, 0.2 to 2.9).

The risk for cleft lip with or without palate was significantly lower for carbamazepine monotherapy than for other antiepileptic drug monotherapy excluding valproic acid (0.1, 0.0 to 0.6) (over half of these cases had recorded exposure to phenobarbital). No significant difference was seen for carbamazepine

monotherapy compared with valproic acid monotherapy (0.3, 0.0 to 2.6), but the point estimate was decreased. The results for diaphragmatic hernia also showed decreased odds ratios but with wide confidence intervals (table 4).

We tested the one additional indication identified in literature, cleft palate, in the EUROCAT dataset, but we did not confirm this indication compared with no antiepileptic drug exposure (crude odds ratio 1.3 (0.4 to 4.1) with non-chromosomal controls) [15].

Exploratory analysis

The exploratory analysis of all malformation subgroups found that all proportions were similar (P>0.05) except for two subgroups: single ventricle (2.3% (n=3) of carbamazepine exposed 0.3% expected, χ^2 P<0.001) and atrioventricular septal defect (3.1% (n=4) of carbamazepine exposed 0.8% expected, χ^2 P<0.011, data available on request). When we removed registrations with these malformations from our non-chromosomal control group, our results regarding the five indication case groups stayed essentially the same.

Discussion

Interpretation of the results

Of the five indications for specific malformations associated with exposure to carbamazepine monotherapy that we identified from published cohort studies, spina bifida was the only confirmed indication (odds ratio 2.6 (1.2 to 5.3) for comparison with no exposure to antiepileptic drug and with the non-chromosomal controls). All other case groups resulted in an odds ratio around or below 1. According to the upper confidence limits, we could exclude 50% of excess risks for cleft lip and hypospadias with some degree of certainty, but further surveillance would be necessary to gain larger numbers to estimate risks for diaphragmatic hernia and total anomalous pulmonary venous return with more precision.

In our analyses comparing exposure to carbamazepine monotherapy with valproic acid monotherapy we found a significantly decreased risk for spina bifida (odds ratio 0.2, 0.1 to 0.6) and hypospadias (odds ratio 0.2, 0.1 to 0.5), indicating that the risk of spina bifida and hypospadias with carbamazepine is less than with valproic acid. In our study of valproic acid we found a six fold risk for spina bifida and a sevenfold risk for hypospadias with valproic acid monotherapy compared with exposure to another antiepileptic drug with the non-chromosomal control group [6].

It is noteworthy that the risk for cleft lip with or without palate was significantly more related to other antiepileptic drug monotherapy (excluding valproic acid) than to carbamazepine monotherapy (odds ratio 0.1, 0.0 to 0.6). Over half of these cases were exposed to phenobarbital, which is known to be associated with cleft lip and palate [17].

Comparison with other studies

The rate of major malformation with exposure to carbamazepine that we found when combining the eight cohort studies (3.3%) was lower than the rate reported in the only meta-analysis in the literature (44/797; 5.5%, 4.1% to 7.3%) [18]. Eleven of the 16 studies included in the meta-analysis contained information about malformations. Three of these 11 presented a case list with specific malformations and were included in our literature review. The difference in the rate of malformations could be explained by dissimilarities in classification of minor malformations for exclusion.

In a general review of the literature, we did not find any strong suggestions of specific malformations other than our five case groups, except for a recently published abstract based on the North American AED Pregnancy Registry, which suggested a 24-fold (7.9 to 74.4) increase in the rate of isolated cleft palate with carbamazepine [15]. In the EUROCAT dataset we did not confirm this strong indication, either in the proportional exploratory analysis or by calculation of odds ratios.

Strengths and limitations of the study

One limitation of our study is that we used controls with malformations. Controls with non-chromosomal malformations will result in an underestimation of the effect if there are any individuals left in the control group with malformations that are related to the exposure. Our exploratory analysis was designed to see if there were specific malformations of concern; we found single ventricle and atrioventricular septal defect to represent a higher proportion than expected (though this might be a chance finding associated with multiple comparisons). When we excluded these two malformations from the control group, our results stayed essentially the same. Chromosomal controls can lead to an overestimation of effect of drug exposure if exposure is not recorded completely because of the lack of relevance of drug exposure in early pregnancy. We have examined this in previous studies of lamotrigine and valproic acid and found no evidence of substantially poorer recording of exposure to antiepileptic drugs for chromosomal controls, either by examination of exposure rates or by examination of information gathering procedures for exposure [6,9]. Exposure information is mainly collected prospectively in medical records and is ascertained by the registry regardless of type of malformation. In a previous study evaluating exposure to valproic acid and specific congenital malformations, we found similar odds ratios for non-chromosomal and chromosomal controls, while in our study of lamotrigine exposure and orofacial clefts, as in the current carbamazepine study, we found greater odds ratios with chromosomal controls than with non-chromosomal control group. One interpretation is that there is a generalized risk of malformation associated with carbamazepine, which is not specific to a few malformation groups. With that interpretation, the

difference in exposure rate between the control groups would suggest an up to 50% generalized increase risk of major malformations with carbamazepine. Another interpretation is that carbamazepine "protects" against chromosomal malformations—for example, by raising the chance of an early miscarriage for affected pregnancies. In relation to the finding regarding spina bifida, we consider that the true odds ratio is likely to be between the estimates obtained from the two control groups.

The apparent specificity of effect of carbamazepine for spina bifida, compared with valproic acid, with a much larger range of effects, might be a useful biological clue in elucidating the underlying teratogenic mechanism. It is also possible that spina bifida is in part related to the underlying epilepsy rather than the drug used, though our results show that the drug used at least affects the level of risk of spina bifida. In this large population based study, we carried out a direct comparison between the risks for specific malformations associated with carbamazepine monotherapy compared with valproic acid monotherapy. A limitation in our comparison of risks between exposure to different types of antiepileptic drug was that we did not have the information to adjust for type of epilepsy, frequency of seizures, used of folic acid, and dose of the antiepileptic drug.

Conclusions and policy implications

Although most antiepileptic drugs taken during pregnancy significantly increase the risk for one or more specific fetal malformations, the occurrence of these malformations is nevertheless rare. Most exposed pregnancies result in a baby without malformation. The best option regarding antiepileptic drug treatment can be chosen only on an individual basis by the woman and neurologist before pregnancy, weighing the benefits of epilepsy control against the risk of teratogenicity. In this study we have confirmed that carbamazepine is less teratogenic than valproic acid. A Cochrane review found no evidence to support the belief that valproic acid is superior to carbamazepine for generalized tonic-clonic seizures [19]. Therefore, we agree with the recent recommendation of the American Academy of Neurology to avoid valproic acid in pregnancy if possible [20]. Our literature review gives a 3.3% risk of major malformations with carbamazepine monotherapy, and our case-control study shows that the major concern is a moderately increased risk of spina bifida. This should to help in decision regarding whether carbamazepine should be the antiepileptic drug of choice in pregnancy.

Acknowledgement

We thank J Morrow, U Kini, F Vajda, and K Wide for providing us with more detailed information about the cases described in their papers [1,3-5] and I Barisic for case review.

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Appendix 1

Crude odds ratios (OR) for antiepileptic drug (AED) and carbamazepine (CBZ) exposure compared to' no antiepileptic drug', valproic acid (VPA) and other antiepileptic drug exposure, using a non-chromosomal malformed control group (C1) and chromosomal control group (C2)

			Carbamazepine monotherapy		
malformation subgroup	exposed		ORcrude [95%CI] vs. no AED	ORcrude [95%CI] vs. VPA mono~	ORcrude [95%CI] vs. other mono^
Spina bifida N=2,048	8	C1	2.7 [1.3-5.5]	0.2 [0.1-0.6]	1.1 [0.4-3.6]
		C2	4.7 [1.9-11.9]	0.4 [0.1-1.2]	1.4 [0.3-6.1]
Total anomalous pulm. v. return N=132	0	C1	-	-	-
		C2	-	-	-
Cleft lip (with or without palate) N=3,544	1	C1	0.2 [0.0-1.4]	0.3 [0.0-2.6]	0.1 [p0.0-0.6]
		C2	0.3 [0.0-2.6]	0.4 [0.0-4.6]	0.1 [0.0-0.9]
Diaphragmatic hernia N=755	1	C1	0.9 [0.1-6.4]	0.4 [0.0-4.5]	0.2 [0.0-2.3]
		C2	1.6 [0.2-12.3]	0.6 [0.1-7.9]	0.3 [0.0-3.4]
Hypospadias, boys only N=5,393	6	C1	0.7 [0.3-1.7]	0.2 [0.1-0.5]	0.8 [0.2-2.7]
		C2	1.1 [0.4-3.3]	0.2 [0.1-0.9]	0.4 [0.1-2.9]

~ *valproic acid exposed malformed excluding malformations associated with valproic acid exposure*

^ *other monotherapy excluding valproic acid*

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Part III

Considerations for treatment practice

6 DOES FOLIC ACID USE DECREASE THE RISK FOR SPINA BIFIDA AFTER IN UTERO EXPOSURE TO VALPROIC ACID?

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PDS 2010;19:803-807

Purpose: Women with child wish are advised to take folic acid supplements to reduce the risk for spina bifida. However, there is less evidence for this protective effect in women using valproic acid. We investigated the effect of folic acid in women exposed to valproic acid in the first trimester of pregnancy.

Methods: A case-control study was performed with data from a population-based registry of congenital malformations. Our cases were spina bifida registrations and all other malformed registrations (excluding folic acid sensitive malformations) were used as controls.

Results: The odds ratios for the effect of correct folic acid use were calculated among antiepileptic drug (antiepileptic drug) unexposed pregnancies 0.5 [95%CI: 0.3–0.7] and among valproic acid exposed pregnancies 1.0 [95%CI: 0.1–7.6].

Discussion: Due to power-reasons, we cannot conclude that folic acid has no effect on the risk for spina bifida among valproic acid exposed pregnancies. Although for antiepileptic drug unexposed pregnancies we found a decreased risk. Results from (animal) studies support a biologically plausible association between valproic acid, folic acid and spina bifida. While folic acid might not be able to reduce the risk for lower spina bifida lesions caused by valproic acid, the use of folic acid might be important to reduce the risk for higher, folic acid sensitive spina bifida lesions. Further research is needed to get more insight in the most effective form and dose of folic acid in women that use valproic acid to reduce the risk for (higher forms of) spina bifida.

Introduction

Folic acid has been proven to reduce the risk of neural tube defects (NTDs) and it also seems to lower other specific malformations [1-2]. In the Netherlands, women wishing to become pregnant are advised to take 0.5mg folic acid from 4 weeks before conception till 8 weeks into pregnancy [3]. Additionally, in some parts of the world but not in the Netherlands, flour is mandatory fortified with folic acid. Due to the fortification and the maternal use of supplements the prevalence of NTDs decreased [4-5]. Although there is evidence for the protective effect of folic acid in the general population, there is still no clear evidence for this effect in women using antiepileptic drugs. Scientific publications report different results of the effect of folic acid use by women using antiepileptic drugs [6-9].

Our objective was to describe and try to understand the effect of folic acid use on the risk for spina bifida in women taking valproic acid during pregnancy compared to those not taking antiepileptic drugs.

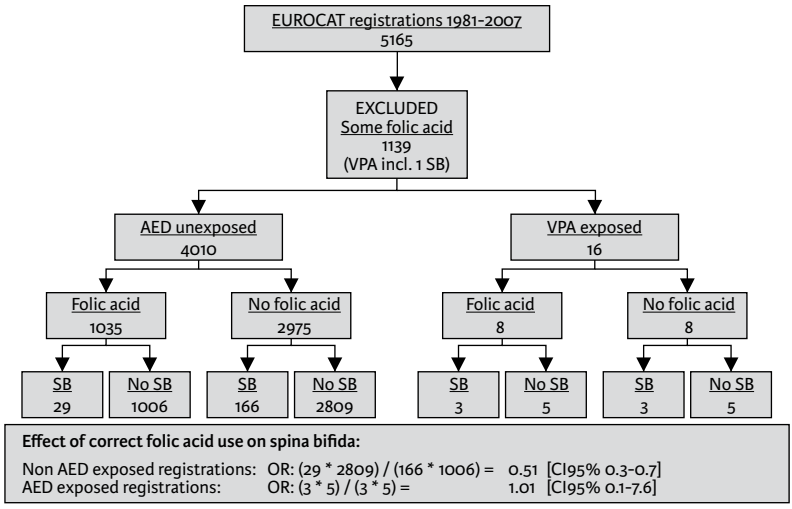
Methods

Setting

We performed a case-control study using data recorded in a population-based registry for congenital anomalies, EUROCAT Northern Netherlands. The methodology for data collection is described in detail previously [10-12]. From this database we created a subset of registrations that were available by July 2008 and born in the period 1981–2007. A registration is defined as a pregnancy outcome with a major malformation registered in EUROCAT. During this study period, 443,165 births took place in the registration area and 12,534 malformed pregnancy outcomes were registered in EUROCAT (including livebirths, stillbirths and terminations following prenatal diagnosis). These figures lead to a major congenital malformation prevalence of 2.8%, which corresponds with the prevalence found in literature (2–3%). Data on folic acid and antiepileptic drug exposure were obtained from pharmacy records and a written and spoken interview with the mother.

Definitions

We selected and validated from the subset of the EUROCAT database all pregnancies in which the mother had a prescription for an antiepileptic drug in the 3 months before pregnancy or during pregnancy, and all pregnancies affected by maternal epilepsy. All registrations with confirmed maternal monotherapy or polytherapy with valproic acid in the first trimester of pregnancy and all pregnancies not exposed to antiepileptic drugs were included. All registrations exposed to antiepileptic drugs other than valproic acid (N=41), all registrations with maternal epilepsy without reported antiepileptic drug use (N=33) and all registrations with missing data on folic acid exposure (N=2,615) were excluded from the analyses. Cases were defined



* *All registrations excluding: folic acid use unknown, maternal epilepsy without AED exposure, and AED exposure not including valproic acid. And excluding folic acid sensitive malformations (cardiac, cleft, limb, NTD and urinary defects)*

Figure 1: decision tree# and odds ratios for the effect of correct folic acid use among AED exposed and unexposed registrations.

as registrations with spina bifida, while all other registrations excluding folic acid sensitive malformations (cardiac defects, clefts, limb defects, NTDs and urinary anomalies (N=4,680)) were used as controls [13].

Folic acid exposure was defined in three groups: no folic acid, some folic acid (including women who used folic acid only for a few days) and folic acid (defined as women using at least 0.4mg folic acid from 4 weeks before conception until 8 weeks in pregnancy) (Figure 1).

Registrations exposed to some folic acid (N=1,139) were not included in the analyses to avoid misclassification, because we do not know the protective effect of folic acid if it is used irregularly or only in a part of the advised period.

Analysis

All included registrations were put into a flowchart, with divisions for valproic acid exposure, folic acid use and spina bifida (Figure 1). Using case-control analyses, we analyzed the effect of folic acid use on the risk for spina bifida in pregnancies exposed to valproic acid and in antiepileptic drug-unexposed pregnancies. In the EUROCAT dataset it is possible to control for maternal age and year of birth, although no significant trend was seen within these variables and we therefore decided not to perform adjustments due to our low numbers. All analyses were performed using SPSS 16.0.

Results

The prevalence of spina bifida in the EUROCAT database decreased over time from 5.2 (1981–1985) to 3.9 per 10 000 (2002–2007). The antiepileptic drug exposure in the dataset was 6.6 per 1000 registrations (83/12 534) in the first trimester of pregnancy and the exposure to valproic acid specifically was 3.4 per 1000 (42/12 534; 34 monotherapy, 8 polytherapy). Over 80% of the antiepileptic drug exposed registrations were exposed to antiepileptic drug monotherapy. The use of folic acid supplements did increase over time and the use was higher among antiepileptic drug exposed registrations.

In total, 5,165 pregnancy outcomes, born 1981–2007, were included in the case-control analyses. A flowchart shows valproic acid exposure, folic acid use and outcome (Figure 1). Folic acid (at least 4 weeks before conception till 8 weeks after conception) was used by 20% of the included registrations, while 58% did not use folic acid at all.

In antiepileptic drug unexposed pregnancies, the use of folic acid reduced the risk for spina bifida by 51% (OR=0.5 [95%CI: 0.3–0.7]).We found no effect of folic acid use in valproic acid exposed pregnancies in relation to the risk for spina bifida OR=1.0 [95%CI: 0.1–7.6].

Looking at the location of the spina bifida lesions, no thoracic or higher located lesions were found among valproic acid exposed cases. We did find higher located lesions among our antiepileptic drug unexposed cases and in this group the location of the lesion tended to be lower in cases exposed to folic acid (Table 1).

Table 1: Location of the spina bifida lesion in valproic acid exposed and antiepileptic drug unexposed, specified for folic acid use (frequencies).

	valproic acid		No antiepileptic drug	
	folic acid	no folic acid	folic acid	no folic acid
sacral & sacral-lumbar	1	1	10	47
lumbar	2	2	10	41
lumbar-thoracic and higher	0	0	5	67
not otherwise specified	0	0	4	11
Total spina bifida	3	3	29	166

Folic acid: use of folic acid supplements from at least 4 weeks before conception until 8 weeks in pregnancy

It is noteworthy that in our total dataset, 7 of the 42 valproic acid exposed women using folic acid during the entire advised period consumed 5mg rather than 0.5mg. None of these women delivered a baby with spina bifida, although 3 of these 7 registrations were excluded in the analyses because of a cardiac defect.

Discussion

We found a reduction in the risk for spina bifida of over 50% among pregnancies

not exposed to antiepileptic drugs, as expected. No effect on the risk for spina bifida in pregnancies exposed to valproic acid was detected. However, based on our low numbers we cannot conclude that folic acid does not reduce the risk for spina bifida in pregnancies with first trimester VPA exposure (OR: 1.0 [0.1–7.6]). However, our findings are in line with the findings in a case-control study performed in the US and a cohort study from the UK [7,9]. Both studies did not find a significant reduction in the risk for NTDs in VPA exposed pregnancies.

If we stratified our valproic acid exposed registrations by consumed dose of folic acid by the mother, no cases of spina bifida were seen among mothers using 5 mg folic acid from 4 weeks before till 8 week during pregnancy or longer. Our numbers were too small to perform meaningful statistical analyses.

We wondered if it would be biologically plausible that folic acid reduces the risk for spina bifida in valproic acid exposed fetuses.

The majority of published studies show that valproic acid does not reduce the total serum folate levels in contrast to enzyme-inducing antiepileptic drugs like carbamazepine [14-16]. Despite the fact that the total serum folate levels are not reduced due to valproic acid exposure, several cases are described in which folic acid use did not protect against spina bifida in case of maternal valproic acid use [6,17-18]. Notable is that the spina bifida lesion in these published cases (N=9) for all specified ones (N=5) is diagnosed as lumbosacral, a lower form of spina bifida [6,18]. The four other published spina bifida cases were not otherwise specified [17]. Also in our study population, the spina bifda cases that were exposed to valproic acid and folic acid have lumbar or sacral forms of spina bifida (Table 1). Among the antiepileptic drug unexposed cases we additionally see higher lesions and it seems to be that higher lesions tend to be more frequent without folic acid use. However, due to our small numbers we cannot perform meaningful analyses.

The theory of the closure of the human neural tube: existing of five closure sites, is well-known although we know that the model is not accepted by all investigators [19-22]. However, according to this model valproic acid is thought to interact with the fusion of closure site 5 (the lowest closure site). Failure in the fusion of this lowest site is thought to be independent of folic acid, in contrast to closure sites 1 (caudal), 2 and 4 [19]. Based on these studies it seems that folic acid is important for women using valproic acid in pregnancy to reduce higher located lesions, but it will not avoid the lower ones.

Is 0.5mg enough or is it better to give 5 mg folic acid to women using valproic acid? In our data we saw no cases of spina bifida in which 5 mg folic acid was used (at least from 4 weeks before pregnancy until 8 week in pregnancy). Due to the low number of registrations in this 5 mg group, we could not perform detailed analysis on dose and thus we cannot conclude that 5 mg daily supplements give a better protection against the increased risk for having a baby with spina bifida in case of valproic acid use. Human data is scarce on folic acid dosing among valproic acid users [3]. Additionally, animal studies do not provide consistent evidence about the effect of folic acid

supplementation [24-27]. Although, in mice models it was discovered that valproic acid inhibited the transfer of the formyl group necessary to convert tetra-hydrofolate into folinic acid (5-formyl tetrahydrofolate) the most active form of folic acid [28-29]. This could explain why the total serum folate levels are not decreased, but the efficacy is. If folic acid stays in a less active form, more folic acid might help to increase the effect. On the other hand, folinic acid is also registered and might be much more effective for women using valproic acid with a child wish (to reduce the risk for higher lesions). Folinic acid or a higher dose of folic acid might be an option, but we need to be aware of possible interactions of folic acid and monitor the efficacy of the antiepileptic drug. However more research is needed to test these theories.

This study focused on the effect of folic acid in valproic acid exposed pregnancies, but it is impossible to see folic acid as an independent factor, because an alteration of one substance within the folic acid cycle influences the whole metabolism. Therefore, it is also important to keep in mind that the decrease in methionine might play an important role in the transmethylation or the decrease in glutathione which is important in the detoxification of radicals [30-34]. Additionally to the effect on the folate metabolism valproic acid interacts with many other pathways as described in a recent study [32-35].

Recently, the American Academy of Neurology published an extensive review concerning the care for pregnant women with epilepsy. One of the main conclusions was to avoid valproic acid in pregnancy if possible, because of the evidence that valproic acid is associated with an increased risk of multiple congenital malformations and developmental delay, and that valproic acid confers a higher risk than other antiepileptic drugs [36-37]. However, for some women valproic acid is the only effective therapy and, above all, most children are born healthy. For those women who are dependent of valproic acid treatment it is very important to perform further research in comparing different doses of folic acid with the effectiveness of folinic acid to reduce the risk for spina bifida and other folic acid sensitive malformations. The best design to test the efficacy would ideally be in a clinical trial. In the meanwhile, women using valproic acid should be recommended to use folic acid, even though the evidence for a reductive effect is scarce, but there is no evidence of harm [23,38].

Despite the folic acid related forms of spina bifida, valproic acid exposed women probably will keep an increased risk for lower located spina bifida lesions.

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7 ECONOMIC EVALUATION OF ANTIEPILEPTIC DRUG THERAPIES IN YOUNG WOMEN; WITH SPECIFIC FOCUS ON TERATOGENIC OUTCOMES

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Objectives: To perform an economic evaluation of the antiepileptic drug choice in young women, with a potential child wish, to estimate the impact of teratogenicity on the costs per quality adjusted life year (QALY).

Methods: A decision-tree model is used to calculate the costs per QALY, taking into account the malformation risk in offspring due to the exposure to carbamazepine, lamotrigine or valproic acid, based on the European birth cohort of 2007. Probabilistic sensitivity analyses were performed using Monte Carlo simulation.

Results: Valproic acid is dominated by carbamazepine after rank ordering on costs. The cost–effectiveness of lamotrigine versus carbamazepine was estimated at €175,534 per QALY. Though valproic acid was dominated by carbamazepine in terms of costs and related effects, it is clinically relevant to compare lamotrigine with valproic acid. In particular, treatment options are dependent on several individual and clinical characteristics and these agents are therefore not always considered as interchangeable for all specified populations. The cost-effectiveness for lamotrigine versus valproic acid was estimated at €13,370 per QALY. With assuming a willingness to pay threshold of €50,000 per QALY, results from the probabilistic analysis resulted in an acceptance level for lamotrigine versus carbamazepine and lamotrigine versus valproic acid of 4% and 99%, respectively.

Conclusion: Based on epidemiological data it is advised to whenever possible avoid valproic acid during pregnancy. Both carbamazepine and lamotrigine are estimated to be cost-effective treatment options versus valproic acid if focused on teratogenicity.

Introduction

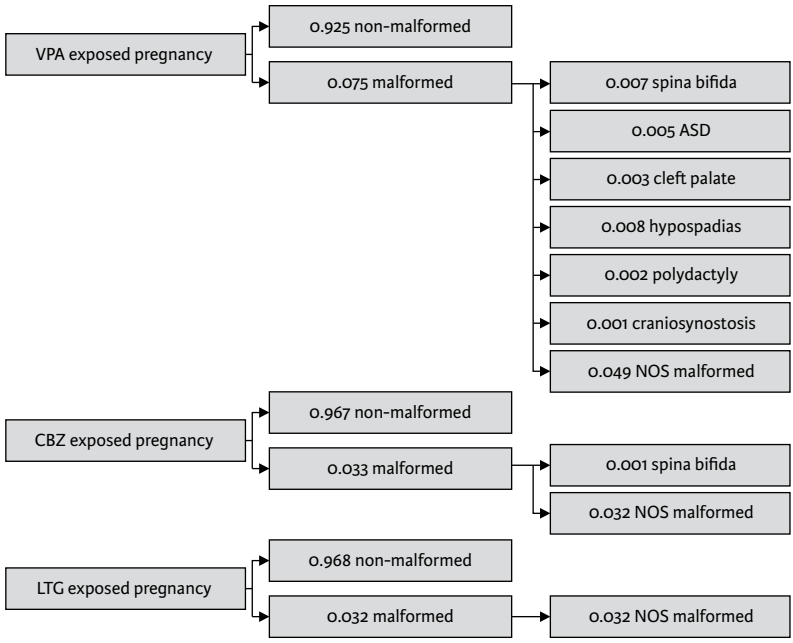
Epilepsy is a chronic disease with age-dependent increase in prevalence. About a half percent of all teenage girls are using antiepileptic drugs [1-2]. A considerable part of these girls are still using the same antiepileptic drug when they have a child wish as switching is not considered to be easy. Therefore, it is important for the prescribers to keep in mind while making the therapy choice that younger girls develop a future child wish with potential implications for the choice of treatment. In pregnancy, around 3.3 per 1000 women are using antiepileptic drugs in the first trimester, the period in which congenital malformations occur [3-4].

Carbamazepine, valproic acid and lamotrigine are the most used antiepileptic drugs, both among pregnant and non-pregnant women [5-6]. All three agents are first choice options for partial epilepsy. However, in case of generalized epilepsy only valproic acid is the drug of first choice and both carbamazepine and lamotrigine are second choice therapies [7-8]. Although a recent Cochrane review could not find evidence to support the belief that valproic acid is superior to carbamazepine in generalized tonic-clonic seizures [9].

Valproic acid is a relatively cheap and very effective antiepileptic drug which is already a successful treatment option in epilepsy for over 40 years. However, it is associated with an increased risk for major congenital malformations compared to other antiepileptic drugs [10]. Maternal use increases the risk for spina bifida, cleft palate, hypospadias, atrial septal defect, polydactyly and craniosynostosis. In contrast, carbamazepine has been shown to be only associated with an increased risk for spina bifida, with a risk even significantly lower than for valproic acid [11]. Lamotrigine on the other hand is more expensive, but up to now not associated to specific malformations [5, 12-13].

It is not ethical to perform randomized clinical trials with pregnant women to estimate human teratogenicity and therefore, all available evidence is derived from post-marketing observational data. In particular, these studies provide less strong evidence and are more sensitive to bias and confounding. Also, it is uncommon to express prevented malformations due to the choice of a specific drug in terms of money. However, in society the willingness to pay for a healthy child is often high and therefore hard to compare to the willingness to pay for an intervention which will add an extra year to individuals' life expectancies. 'Interventions' with a higher willingness to pay are certainly not uncommon for economic analyses considering safety risks (e.g. blood products) [14]. Also, the general willingness to pay to avoid health losses is greater than the willingness to pay for health gains [15].

The aim of this study is to perform an economic evaluation for antiepileptic drugs initiated in young women, with a potential child wish, applying the societal perspective and focusing on safety in the offspring rather than efficacy.



NOS, not otherwise specified

Figure 1: Decision tree, prevalence per specific malformation associated with valproic acid (VPA), carbamazepine (CBZ) and lamotrigine (LTG) [5, 10-11].

Methods

Data and Assumptions

Based on the EUROCAT *Antiepileptic Study Database* the prevalence for major congenital malformations in the general population is around 2.8% [12]. This prevalence increases in case of maternal carbamazepine (3.3%) [11], lamotrigine (3.2%) [5] or valproic acid (7.5%) [10] exposure. The decision tree for specific malformations associated with antiepileptic drug use is presented in figure 1. Some specific malformations are increased by these antiepileptic drugs however it does not explain the total prevalence. The unexplained part is defined as 'not otherwise specified' (NOS).

Health Gains

Teratogenicity of valproic acid is higher than for other treatment options in epilepsy. However, for each patient the best therapy can only be chosen by the neurologist and the patient, but in case there are more possible treatment options valproic acid might not be the drug of first choice in women with child

bearing potential as teratogenic risks for other antiepileptic drugs seem to be lower [10-11]. Prevention of teratogenesis with considering potential risks at therapy initiation will therefore result in lifetime health gains.

For all associated malformation subgroups we estimated the quality of life and the life expectancy based on the published literature (*table 1*) [16-31]. For our 'rest group' of not otherwise specified malformations it was not possible to find any reference. Therefore we took the quality of life of pregnancy outcomes with an extreme low birthweight as a proxy (0.97) in the base case analysis [23]. This assumption was varied in both univariate (to see how sensitive the analysis is for this parameter) and probabilistic sensitivity analysis.

Costs

We assumed lifetime use of antiepileptic drugs starting at age 15. Based on European life tables, we estimated the lifetime costs for the three antiepileptic drugs in 2010 Euros,: carbamazepine (dose 1000mg/day) €2,707, lamotrigine (dose 300mg/day) €11,329 and valproic acid (dose 1500mg/day) €3,694 [8, 32*]*. These values were based on Dutch prices and costs were discounted at 4%.

Lifetime costs for each of the specific malformations were estimated based on published literature. All costs are presented for 2010 euro's. If costs were originally calculated in another currency or from another year we used the historical exchange rate and inflation correction [33-34]. Table 1 gives an overview of all lifetime costs per malformation subgroup.

Cost-effectiveness and Cost-utility analysis

In the cost-effectiveness analysis the net costs per quality adjusted life year (QALY) were calculated comparing the three antiepileptic drugs, by dividing the difference in the 'total net life-time costs' by the sum of the difference in respectively the 'total life years lost' and the 'total quality of life lost' (presented in table 2). All costs and health gains were discounted following the Dutch guidelines for conducting pharmacoeconomic studies with 4% and 1.5%, respectively [35].

The analysis is performed based on the European Union (27 countries) birth cohort of 2007 which consist of 5,285,057 live births (49% male) and the average life expectancy at birth of this cohort: 79.2 year [*32*]. As the prevalence of first trimester exposure to antiepileptic drugs is around 3.3 per 1000 about 17,441 pregnancies of the EU 2007 birth cohort were expected to be first trimester exposed [3-4]. We calculated the total costs and effects based on assuming that all 17,441 women used carbamazepine, lamotrigine or valproic acid. For our model, we assumed equal effectiveness of the three drugs in all women. We know that in practice this is not the case due to difference in severity, type of epilepsy and interpersonal differences. However, it is difficult to account for such hetereogeneity and all three drugs have proven to be effective in the most common types of epilepsy [7, 9].

Probabilistic analysis was conducted to estimate uncertainty around the lifetime costs of the malformations, the prevalence of the specific malformations and the QALYs and LYL per treatment option were taken into account. Incremental cost-effectiveness planes were constructed based on Monte Carlo simulation (10000 replicates) to test the robustness of the health economic outcome. Additionally, cost-effectiveness acceptability curves were derived to estimate the probability of acceptance with varying willingness to pay thresholds.

Table 1: Quality of life (QALY) and life years lost and the lifetime costs per case for the associated malformation subgroups for the base case [16-31].

Malformation subgroup	QALY loss (1.5% disc)	life years lost (1.5% disc)	Lifetime costs per case (4% disc)
Spina bifida	20.3	15.1	€ 138,964
ASD	0.4	0	€ 6,591
Cleft palate	1.3	0	€ 13,345
Hypospadias	0.8	0	€ 5,890
Polydactyly	0	0	€ 893
Craniosynostosis	5.0	0	€ 14,990
NOS malformation	1.2	4.9	€ 94,052

Results

Table 1 presents the estimated loss in quality of life and life expectancy together with the expected lifetime costs per malformation. These estimates are derived from various published studies [16-31]. It is estimated that 3.3% or 17,441 pregnancies of the European birth cohort 2007 are exposed to antiepileptic drugs. The total number of malformed pregnancy outcomes, life-expectancy and quality of life estimated for these 17,441 pregnancies are shown in table 2. The general risk for malformations is 2.8% which would result in 493 malformed pregnancy outcomes. This background risk is presented in the first column. The expected number of malformations, life time costs for the three antiepileptic drugs, calculated for the whole birth cohort, and the total life years and quality of life lost are presented the second to fifth column. Medical costs are estimated based on the estimated costs per case as presented in table 1 weighted with the prevalence of each malformation (figure 1). The analyses are performed based on the incremental estimates compared to the background risk.

If the three drugs are rank ordered on costs, one can directly see that valproic acid is dominated (higher costs and more quality of life losses than carbamazepine). From an economic point of view, due to the dominance, valproic acid would not be considered as a first choice treatment option. However, as the indications for the three drugs are not exactly the same and therefore not 100% interchangeable, the cost-effectiveness is calculated for both lamotrigine versus

carbamazepine and lamotrigine versus valproic acid. The cost-effectiveness of lamotrigine versus carbamazepine and lamotrigine versus valproic acid were estimated at €175,534 and €13,370 per QALY, respectively.

Table 2: Total net costs (4% discounted) and effects (1.5% discounted) for carbamazepine, lamotrigine and valproic acid for the European birth cohort of 2007 (17,441 exposed births) the background risk is presented in the first column.

	Background risk	carbamazepine	lamotrigine	valproic acid
N malformed	493	579	566	1247
Total costs malformation	€ 46,393,507	€ 55,642,951	€ 53,241,218	€ 100,702,189
Life time costs drug	€ 0	€ 47,206,615	€ 197,583,337	€ 64,418,409
Total net life-time costs	€ 46,393,507	€ 102,849,566	€ 250,824,555	€ 165,120,598
Total life years lost	2417	3104	2774	6110
total quality of life lost	591	1192	679	3752

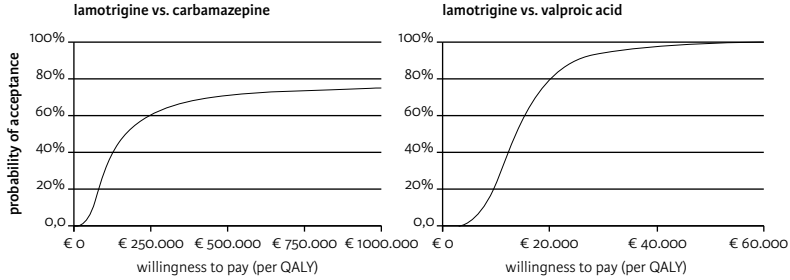


Figure 2: Incremental cost-effectiveness planes for lamotrgine versus carbamazepine and versus valproic acid.

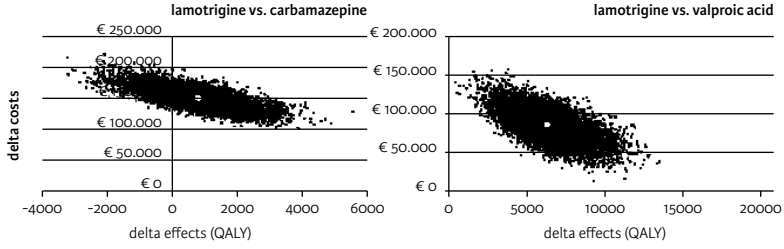


Figure 3: Cost-effectiveness acceptability curves for lamotrigine versus carbamazepine and lamotrigine versus valproic acid.

Table 2 shows that the antiepileptic drug price is the main driver of the cost-effectiveness. In particular, this is caused by lifetime use of these agents. The price of carbamazepine and valproic acid are quite stable over recent years. In contrast, the price of lamotrigine still decreases. If the prize of lamotrigine would decrease with 50%, it could be considered as cost-saving if compared to valproic acid. Also, the cost-effectiveness ratio for lamotrigine versus carbamazepine would decrease to around €60,000 per QALY in such a scenario.

Although there were limited sources for quality of life data for specified and not otherwise specified malformations (NOS) the outcomes were quite robust. In particular, results remained essentially unchanged with increasing or decreasing the estimated QALY loss and life years lost with 50% (€170,168-184,074 per QALY for lamotrigine versus carbamazepine and €11,685-14,793 per QALY for lamotrigine versus valproic acid).

In figure 2 the incremental cost-effectiveness planes are presented for both lamotrigine versus carbamazepine and lamotrigine versus valproic acid. All estimates for the comparison of lamotrigine versus carbamazepine are located in the northern quadrants, with the highest density in northeast. For the comparison of lamotrigine versus valproic acid all estimates are located in the northeast quadrant, indicating a better quality of life for additional costs.

As there is no formal willingness to pay threshold in the Netherlands, cost-effectiveness acceptability curves are calculated to estimate the probability of acceptance for different willingness to pay thresholds in figure 3 [36]. With considering a willingness to pay threshold of €50,000 per QALY, the probability of the acceptance for lamotrigine versus carbamazepine and lamotrigine versus valproic acid were estimated at 4% and 99%, respectively. The median cost-effectiveness is estimated at €173,353 per QALY for lamotrigine versus carbamazepine and at €13,548 per QALY for lamotrigine versus valproic acid.

Discussion

Carbamazepine, lamotrigine and valproic acid are all first-choice therapy options in the treatment of partial epilepsy. In general, valproic acid is widely used, but from a health economic point of view it would not be a first-choice therapy option for women with a potential child wish with partial epilepsy as it is dominated by carbamazepine. Lamotrigine results in better quality of life outcomes in the offspring at higher costs of €175,534 per QALY. This could be interpreted as unfavorable. However, we should keep in mind that economic evaluations based on solely safety outcomes of drugs for the next generation could might be comparable to other economic evaluations in which safety is important, for example, blood transfusions. In this field, interventions are still implemented with a net cost of several millions per QALY [14]. These estimates are very conservative mainly as they do not take into account

that these drug costs cover all costs for mother independent of the number of children. If a woman delivers two children, the drug costs can be divided by two. Additionally, we took into account the lifetime drug costs starting at age 15. The cost-effectiveness ratio would change in favor of lamotrigine if we would only count the fertile years. This method could also be advocated as this is the period in which the 'event' takes place. However, as switching increases the risk to get a relapse we choose to take lifetime drug costs for one drug being used consistently.

In the analyses, we assumed that the three drugs are equally effective in all women who require these antiepileptic drugs. This does not necessarily correspond with the daily practice situation as, for example, not all women will receive the standard dose. Therefore, in daily practice the therapy choice should be made on an individual level based on effectiveness which is dependent on several factors and an uncontrolled woman is probably more expensive. Therefore, despite the dominance, valproic acid will not be ruled out as an alternative treatment option in clinical practice as valproic acid is a very effective drug with a lot of treatment experience. It is also true that there is a subgroup of women that only successfully respond to valproic acid and for some specific types of epilepsy, valproic acid might be considered as the best, or even the only, treatment option. Looking at the indications, lamotrigine is for some types of epilepsy more comparable to valproic acid than carbamazepine. Therefore, we also calculated the cost-effectiveness ratio for lamotrigine versus valproic acid, resulting in €13,370 per QALY, which can be conceived as a favorable cost-effective ratio.

We did not include effects on the cognitive development of the children. Valproic acid exposure during pregnancy has been associated with a lower IQ in the child [37]. No evidence exists for a comparable cognitive effect for carbamazepine or lamotrigine. Notably, as lamotrigine is a newer drug there is no data yet available on the school performance of children exposed to lamotrigine. Additionally, lower IQ could possibly result in less contribution to society over lifetime (e.g. production losses). The same holds true for some of the malformations (e.g. spina bifida). Potential production losses and related losses in tax contribution in the next generation are nicely described in the field of assisted reproduction [38]. For this case it would be the additional costs for a more expensive drug instead of the costs for IVF and it would be the additional expected tax due to a higher IQ or no physical disability potentially resulting in favorable outcomes on the long run.

Notably, only limited evidence exists on the parameter assumptions for the economic evaluation. The available studies presenting quality of life and life

expectancy data were based on various methods. Also, cost data were derived from several studies performed all over the world. Apart from acknowledging this limitation and justify these assumptions as the best there is, we feel that this analysis also nicely illustrates one of the major problems in performing economic evaluations in the field of teratology research. For example the estimates for the lifetime costs for any malformation are based on a study which took into account only 16 different malformations (accounting for 33% of the prevalence of all major malformations)[12].

Pharmacoeconomic analyses are not common in the field of teratology, but could help to make initial therapy choices taking into account potential safety risks for the offspring. From the current analysis, it becomes clear that there are still a lot of important methodological issues left that need to be discussed further. In this paper the analysis is performed for a specific birth cohort. Analyses taking into account the risk for malformations need to be based on large numbers as the prevalence of major malformations is only around 3% of all births, which correspondingly could require economic analysis based on multiple cohorts. Furthermore, an imminent question relates to the willingness to pay threshold for avoiding teratogenic risks in offspring; in particular, is this comparable to that for drugs improving the quality of life of the actual consumer? Finally, one might ask what the optimal data sources are for this type of research.

Ideally most assumptions are derived from clinical trial data, however these study designs are unethical to use for estimating teratogenicity of drugs. Information has to be derived from observational studies. For economic evaluations information is required on the association between a specific drug and a specific malformation. Cohort studies often do not have enough power to provide a precise estimate, but results of case-control studies are often more difficult to use in economic analyses.

In short, based on epidemiological data it is recommended to avoid valproic acid exposure during pregnancy due to a higher risk of teratogenicity [39]. Also from a health economic point of view the use of the less teratogenic antiepileptic drugs, carbamazepine and lamotrigine, is estimated to be cost-saving and cost-effective, respectively. This definitely holds true if analyses investigating teratogenicity are interpreted as interventions to enhance safety [14]. The cost-effectiveness of such interventions directed at safety and averting losses in quality of life are generally interpreted differently with much higher willingness to pay. Therefore policy makers and those controlling the budgets should look further than drug costs and adverse effects in the actual consumer if it concerns women with child bearing potential. In clinical practice, this information seems in line with the epidemiological data

showing that for women with childbearing potential, valproic acid might not be the best first treatment option. However, the best treatment option can only be made on an individual tailor-made base and does not only rely on health economic outcomes.

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GENERAL DISCUSSION

Utilization of antiepileptic drugs around pregnancy

Teratogenicity of drugs is a highly relevant issue for the majority of women with a child wish. As presented in *chapter 1* almost 80% of all pregnant women received at least one prescription for a drug during pregnancy. More than half of these prescriptions are for pregnancy related symptoms and most of these drugs are considered to be safe (= drugs that have been taken by a large number of pregnant women and women of childbearing age, without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed). The remaining half can be categorized into drugs used for chronic conditions and drugs for occasional and short-time use. The risks of both of these groups of drugs are more frequently undetermined or (potentially) harmful. Therefore, it is important that women try to plan their pregnancy and discus with their health care provider if they need (to continue) the drug for their condition and if so, what would be the best treatment option in their situation before they get pregnant.

In case of antiepileptic drugs, most women do need to continue their drug use during pregnancy. However, as described in the introduction this depends on the indication for which the antiepileptic drug is used. As described in *chapter 2*, the prevalence of the use of antiepileptic drugs varies between (European) countries. The prevalence of at least one prescription for antiepileptic drugs during pregnancy varied between 4.0 and 5.2 per 1000 pregnancies for the included countries as presented in *chapter 2*. Also, it was found that use of specific antiepileptic drugs varied between the country-specific pregnant populations.

The reason for performing this study was that the proportions of specific antiepileptic drugs varied between the local EUROCAT congenital malformation registries. The total number of antiepileptic drug exposed registrations per registry is low which raised the question whether the difference between the registries was due to these low numbers or due to a difference in treatment practice between European countries. *Table 1* shows the proportions with 95% confidence intervals of the most frequently prescribed antiepileptic drugs among the general pregnant population (based on data of *chapter 2*) and for the EUROCAT registries located in the same country.

Table 1: Proportion and 95% confidence interval of the most frequently prescribed antiepileptic drugs in the general pregnant population and among pregnancies resulting in a malformed outcome (EUROCAT)

	France*		Netherlands^		Italy#	
	General N=504	EUROCAT N=110	General N=121	EUROCAT N=38	General N=740	EUROCAT N=29
carbamazepine	5% [3-6%]	10% [2-18%]	40% [32-49%]	29% [15-43%]	25% [22-28%]	10% [0-21%]
clonazepam	30% [26-34%]	6% [0-12%]	5% [1-9%]	3% [0-8%]	12% [10-15%]	3% [0-10%]
lamotrigine	11% [8-13%]	14% [4-23%]	3% [0-6%]	5% [0-12%	6% [5-8%]	3% [0-10%]
phenobarbital	2% [1-3%]	-	-	-	15% [13-18%]	28% [11-44%]
valproic acid	23% [19-26%]	47% [33-61%]	26% [18-33%]	45% [29-61%]	11% [8-13%]	28% [11-44%]
other monotherapy	14% [11-17%]	4% [0-9%]	9% [4-14%]	5% [0-12%]	17% [15-20%]	10% [0-21%]
polytherapy	16% [13-20%]	20% [9-31%]	17% [10-23%]	13% [2-24%]	14% [11-16%]	17% [3-31%]

* *comparing the region of Midi-Pyrenees (data '03-'08) with the region of Paris (data '02-'08) plus the region of Strasbourg (data '02-'04)*

^ *both data comes from the same region in the northern part of the Netherlands (data general '95-'09, EUROCAT '95-'07)*

\# *comparing the region of Emilia Romagna (data '04-'07) with the regions Emilia Romagna (data '03-'08) plus the region of Tuscany (data '03-'08)*

In particular, the proportion of valproic acid exposure is higher among malformed pregnancy outcomes, for the countries included in this study. This was in line with the expectations as valproic acid has been reported to be the strongest teratogenic agent out of commonly used antiepileptic drugs (based on experience up until now) [1-5]. Though these are descriptive results, it is hard to identify other trends within this table. The proportions vary both between and within countries, which can be partly due to the low numbers, but figures in published literature show similar variations. The top three of most used antiepileptic drugs around pregnancy in a hospital based cohort study in Denmark (data '96-'00) were lamotrigine (35%), oxcarbazepine (25%) and valproic acid (20%) [6]. The most reported antiepileptic drugs in the Australian Pregnancy Registry of Antiepileptic drugs (data '99-09) were carbamazepine (29%) lamotrigine (23%) and valproic acid (21%) [7]. Over half of the women exposed to antiepileptic drugs during pregnancy in a population-based cohort study in Sweden (data '95-'01) used carbamazepine (56%), valproic acid and phenytoin were reported for 25% and 10%, respectively [4]. In the UK Pregnancy Registry carbamazepine (38%), valproic acid (31%) and lamotrigine (28%) were the most reported (data '96-'05) [1]. It has to be

emphasized that the methods used within the cited studies and the years of data collection were not the same and that the inclusion in the Danish study was based on a diagnosis of epilepsy (instead of use of antiepileptic drugs) The more recent studies show that the second generation antiepileptic drugs are more commonly used in the recent years [8-9]. As guidelines include available evidence from all over the world, one would ideally expect these proportions of specific antiepileptic drug use to be comparable between countries. However, the variation between countries clearly shows how difficult it is to change daily practice in concordance with constantly updating scientific evidence [10]. Non-adherence to clinical guidelines is widely identified across health services [11]. It therefore, seems that doctors rely on their own experience and interpret new evidence slightly different. Several interventions are developed and evaluated to improve the adherence to prescribing guidelines. Computer-based interventions providing reminders during a consultation are likely to be effective in the improvement of clinical performance and change a health care professionals' behavior [12-13]. Prescribing of drugs during pregnancy can be seen as a preventive health care service and these guideline reminder systems have been found effective in this field of care [14]. In case of antiepileptic drug use and the risk for teratogenicity, the reminder could be given based on characteristics such as gender and age.

Teratogenicity of antiepileptic drugs

Antiepileptic drugs can be split into first and second generation drugs. First generation antiepileptic drugs are all antiepileptic drugs that were introduced on the market before the nineties and second generation agents are those approved since the nineties. In general, more experience exists with first generation drugs as these agents are available for a longer period of time. Lamotrigine is the most often used second generation antiepileptic drug and is the drug with most information available about the use around pregnancy of the second generation drugs.

Lamotrigine is marketed as treatment for young women with epilepsy and a (future) child wish. Previous results of Antiepileptic drug & Epilepsy registries in Australia, UK and the US, displayed no evidence that the general teratogenicity of lamotrigine was not comparable with the risk in the general population [1,7,15]. Combining the 2,675 lamotrigine monotherapy exposed pregnancy outcomes described within all published prospective cohort studies gives a general malformation rate of 3.0% [2.3-3.6%] (including possible overlap between some cohorts) [1,4,6-7,15-19].However in 2006 an FDA warning was issued based on a conference abstract presenting a 24-times increased risk for isolated orofacial clefts and 32-times for cleft palate in specific [20-21]. The EUROCAT network tested the indication for an elevated

risk for isolated orofacial clefts using a study population covering about four million births including almost hundred thousand pregnancy outcomes with a major congenital malformation (chapter 3). Despite the large dataset only two lamotrigine monotherapy exposed cases with an isolated orofacial cleft, of which one cleft palate, were included in the analyses. This nicely illustrates the major problem within the research field of teratology: power!

With the data included no evidence was found for an increased risk for isolated orofacial clefts (0.80 [0.11-2.85]) or isolated cleft palate in specific (1.01 [0.03-5.57]) for lamotrigine monotherapy exposure in the first trimester of pregnancy, relative to other malformations. Although the point-estimates were close to 1 the upper limits of the confidence intervals still included a possible moderate risk [22]. To estimate the risk of orofacial clefts relative to other malformations more precisely and to further explore whether lamotrigine exposure may be associated with other malformations, a follow-up study was initiated with yearly updates for five years.

The explorative analyses of chapter 3 showed an indication for club foot. This indication requires further investigation, especially as club foot is a complex malformation which can be related to other malformations (like spina bifida) and which is associated with specific risk factors (e.g. smoking and family history). However, the signal has to be interpreted with caution as one should expect to find something in case of multiple testing.

Although lamotrigine monotherapy may increase the risk of club foot, the drug seems to be relatively safe in pregnancy. Both valproic acid and carbamazepine are associated with spina bifida and valproic acid is also associated with several other malformations (chapter 4 and 5). Spina bifida is generally considered to be a more severe malformation than a cleft (or a club foot). The risks for specific malformations associated with other antiepileptic drugs are mostly unknown.

As there are no save antiepileptic drug alternatives it is very important in which way study results and conclusions based on generally small studies are presented and communicated [2,23-24]. It is important to publish all available information, although unconfirmed indications should be placed in context and tested/confirmed as soon as possible. This could help in preventing unnecessary doubts and fears of patients and health care professionals (here, neurologists). Ideally, indications are tested as quickly as possible and the results should be available in the public domain (e.g. publications). The study design used in the studies presented in the chapters 4 and 5 are examples of this. Moreover, in these chapters both, the in published literature identified indications and the results of the 'confirming' studies, are presented in one paper. In chapter 4, 14 indications for specific malformations that are associated with valproic acid monotherapy, were identified from literature.

Using a case-control design only 6 of these signals were confirmed. In a similar study on carbamazepine only 1 out of the 5 indications for specific malformations identified from published literature were confirmed.

Another way to investigate the effects and impact of teratology is to express prevented malformations associated with the choice of a specific drug in terms of money. In chapter 8 a cost utility analysis is performed to estimate the differences in costs and health gains if all pregnant women that require antiepileptic drugs would take carbamazepine, lamotrigine or valproic acid. Carbamazepine is not a first choice option for all types of epilepsy; however, if suitable this drug could be considered as a good treatment option as there is a lot of experience with this drug. Furthermore, it seems that carbamazepine is relatively safe in terms of teratogenicity and the drug is cheap. From a health economic point of view valproic acid would not be considered as a first choice treatment option if carbamazepine is indicated too, due to dominance. Lamotrigine seems to give a higher quality of life to the offspring, but this drug is more expensive. Estimated costs per QALY were €175,534 compared to carbamazepine and €13,370 compared to valproic acid, assuming equal effectiveness of these three drugs. These estimates are very conservative mainly as they do not take into account that these drug costs cover all costs for mother independent of the number of children. If a woman delivers two children, the drug costs can be divided by two. Additionally, these rates are expected to change in favor of lamotrigine as the prices of lamotrigine are decreasing every year (at least in the Netherlands). The extra money spent to prescribe life-long lamotrigine instead of valproic acid will avoid almost 700 babies to be born with a major congenital malformation in Europe, annually (assuming equal effectiveness of both drugs).

Regardless the methods used for exploration and investigation of the risks and consequences of malformations associated with antiepileptic drugs, in the end the choice for the best treatment for a woman can only be made on an individual basis. However, it is generally wise to follow the advice of the American Academy of Neurology which recommends avoiding valproic acid during pregnancy if possible [25]. Switching between antiepileptic drugs is not easy, and it would therefore also be recommendable not to start with valproic acid in newly diagnosed girls/women with a (possible future) child wish. In this thesis, only major congenital malformations are taken into account. In daily practice also risks for minor malformations and behavioral effects, which are possibly more common than major malformations, will influence the therapy choice [26-27]. Furthermore, if women using antiepileptic drugs have a preconception discussion with their neurologist, it is important to recommend folic acid use from at least 4 weeks before conception till 8 weeks

in pregnancy. In the general population, it is estimated that the risk for a baby with a neural tube defect is reduced with approximately 65% if a women used 0.4-0.5mg folic acid supplements daily in the recommended period [28-29]. Only women who previously delivered a child with a neural tube defect are advised to take 5 mg around subsequent pregnancies in the Netherlands. The Dutch advice for women using antiepileptic drugs is to take the normal dose, whereas in some countries these women are advised to take 5 mg of folic acid [30-33]. Also the summary of product characteristics of valproic acid recommends women using valproic acid to use 5 mg folic acid [34]. While no conclusive evidence exists for the effectiveness of this higher folic acid dose, this policy is often explained by the fact that some of the antiepileptic drugs have folic acid antagonistic effects [34-35]. In chapter 6, the preventive effect of folic acid on spina bifida was estimated for valproic acid exposed pregnancies. No evidence was found for a protective effect: OR 1.0 [0.1-7.6], but the confidence interval is wide. Although, not accepted by all investigators, there is a theory explaining the absence of the protective effect. According to this theory the neural tube exists of five closure sites of which folic acid is involved with the closure of sites 1 (caudal), 2 and 4. Valproic acid is thought to interfere with site 5 (the lowest closure site) which closes independently of folic acid [36]. If this theory holds true it explains the more prevalent lower lesions among women who delivered a child with spina bifida while using valproic acid [37-38]. As the prevalence of spina bifida is 13-times increased among valproic acid exposed pregnancies (chapter 4), it is very important for women requiring valproic acid to collect more evidence on the effect of folic acid. In particular, it is important to investigate further the mechanisms of action on the spine of both folic acid and valproic acid.

As stated in the introduction section of this thesis, health care professionals are more likely to prescribe drugs with more experience in pregnancy rather than newer drugs in women with a child wish. This also holds true for antiepileptic drugs. On the one hand this seems logical, as we do not know the size of the teratogenic risk for the second generation antiepileptic drugs. On the other hand this does not seems logical, as we do know that the first generation antiepileptic drugs do increase the risk for major congenital malformations. Among data available for the second generation antiepileptic drugs it is mainly topiramate being associated with a specific malformation. Data available up till now show more cleft cases than expected, which resulted in an FDA label change in March 2011 [9,39-40]. This association will be tested in case-control studies in Europe using the EUROCAT Antiepileptic Study database and the US using data of National Center of Birth Defects and Developmental Disabilities and Slone Epidemiology Center.

Within EUROCAT, the proportion of malformed pregnancy outcomes exposed to second generation antiepileptic drugs increases in the most recent years, but the absolute numbers per individual antiepileptic drug are still small. Therefore it is hard to perform analytical studies on specific malformations with sufficient power. The reason for these small numbers could be preference for older antiepileptic drugs with more experience in pregnancy or these second generation antiepileptic drugs are less teratogenic. For a potential safe (future) antiepileptic drug it will be very hard to perform a study within EUROCAT as it will take many years to include enough pregnancy outcomes for sufficient power.

For example, the risk for a major congenital malformation in the general population is around 3 per 100, the use of any antiepileptic drug in pregnancy is around 4 per 1000 which means that you will need about 8333 pregnancies to expect to find 1 major malformed outcome exposed to antiepileptic drugs in case of no increased risk. This is not even taking into account the specific antiepileptic drugs. For most second generation antiepileptic drugs, the prevalence of monotherapy is around 0.5 per 1000 (or even less) which means that it approximately requires 66,666 pregnancies to identify one major malformed pregnancy outcome exposed to the antiepileptic drug of interest for an antiepileptic drug that does not increase the risk of malformations. In other words you would in this case expect only 3 malformed pregnancy outcomes exposed to the drug of interest per year in the total Dutch birth cohort (≈180,000). This is not even taking into account the prevalence of a specific malformation.

To have a good impression of the maternal drug use in the general pregnant population (and not only among those with a malformed outcome), it is very valuable to include non-malformed pregnancy outcomes in EUROCAT. As long as non-malformed outcomes are not registered, it is valuable to perform population-based drug utilization studies in the EUROCAT region. These non-malformed controls or these utilization studies can provide an estimate of the prevalence of exposure to specific antiepileptic drugs in the general pregnant population and will help to estimate the frequencies you can expect within EUROCAT.

Control groups, bias and confounding

Within the EUROCAT network information is available for live born, still born and terminated (after prenatal diagnosis) pregnancy outcomes with major malformations. In case-control studies, we use malformed controls not associated with the exposure under study. The odds ratios calculated in chapter 3, 4 and 5 are presented compared to other malformed pregnancy outcomes, rather than compared to the general population. In other words these analyses relate more to specificity of effect rather than the effect size as a whole.

Non-malformed control groups can be very valuable, as these groups offer the opportunity to calculate the risks relative to the risk in the general non-malformed population. This effect-size is easier to interpret. However, not all non-malformed control groups are appropriate. The control group needs to be representative for the general population (or the sub population). This is not always the case as it is hard to deal with selection and information bias.

Due to the criticism in literature it was decided to collect a non-malformed control group that could be used in case-control studies with the Dutch EUROCAT [41-43]. Since 2004, non-malformed pregnancy outcomes were collected in the northern Netherlands with the aim to gather drug exposure information of a non-malformed control group. However, the control group turned out to be not representative [44]. Especially the low prevalence of drug use can be considered as a problem in pharmacoepidemiological case-control studies. If we would have used this non-malformed control group it would lead to an overestimation of the risk (in case of OR>1) and we would therefore detect false associations. The results of this evaluation strengthened our feeling that a control group is not just good because it is a non-malformed group.

For the choice of 'our' control group it is more important that exposure to drugs is representative than the fact that the control group consists of non-malformed pregnancy outcomes. Especially, because using malformed controls can help to reduce recall bias, which is a problem with retrospective studies like case-control studies. Although the evidence supporting the effect of recall bias is inconsistent, some studies found differences in their recall of exposures in pregnancies resulting in non-malformed outcomes compared to mothers delivering a malformed child [45-46]. The risk for recall bias depends on the way the exposure data is collected. Exposure data based on questionnaires is most sensitive, although the design of the questions can help to reduce the bias [47]. However, since most drug exposure information was recorded in medical records before the pregnancy outcome was known, recall bias seems unlikely for the case-control studies included in this thesis.

Ideally, one would use a non-malformed, a genetic and a non-chromosomal malformed control group which are all collected in the same population-based system. The non-malformed group is sensitive for recall bias and selection bias if only a sample of the non-malformed pregnancy outcomes is included. Underreporting of drug use will lead to an overestimation and an unrepresentative sample can both lead to an over- or an underestimation of the investigated relative risk. The two malformed control groups (gathered using the same methods in the same registry) are less sensitive to recall bias as both groups of mothers will feel responsible (guilty). However as genetic malformations are assumed to be unrelated to drug exposure this group is

more sensible for information bias as the exposure information might be less complete (as the collection of these data might seems less important). The non-chromosomal control group on the other hand might give an underestimation of the relative risk if malformations that are associated with the exposure of interest are included in the control group. This last point could also be true for the chromosomal controls: valproic acid exposure is associated with ASD (chapter 4) and pregnancy outcomes with chromosomal malformations have an increased risk for ASD. However, in case of valproic acid exposure and a chromosomal pregnancy outcome the ASD could be related to both; the drug or the genetic malformation.

Chapters 4 and 5 raise another point that needs to be mentioned here: some of the malformation subgroups that were cases in the valproic acid study were controls in the carbamazepine study. This was no problem in the comparison of carbamazepine with 'no antiepileptic drug use'. However, in the direct comparison between carbamazepine and valproic acid this resulted in a relation between 'unexposure' (=valproic acid exposure) and some subgroups included in the control group. It is important to not only exclude malformation subgroups associated with the exposure under study (=carbamazepine) from the control group, but also those associated with 'unexposure' (=valproic acid). If we would have included these related malformations, this could have led to an underestimation of the risk (in the analysis of spina bifida, odds ratios below 1).

Confounding factors are important to take into account. Although within the case-control studies presented in this thesis we were not able to adjust for all factors one would like to adjust for, for two reasons: low numbers or no information about the specific characteristic. In our analyses we adjusted (if possible) for maternal age, year of birth of the child and reporting local registry.

If we would have had (complete) data on folic acid use, family history, type and severity of epilepsy and dose information of the antiepileptic drug it would be important to investigate the influence of these characteristics and to take them into account (if possible with regard to the numbers). Especially information about the dosage used would be very important as more and more evidence is available showing higher risks for higher dosages of antiepileptic drugs [1,3,5,48-49].

In case-control studies the odds ratio is a good approximation of the relative risk if the outcome is infrequent. This is the case for (specific) malformations and therefore the outcome can be interpreted as a relative risk: it presents the risk for an event in the exposed group compared to the risk for this event in an unexposed group. It is not possible to use a case-control study to calculate an absolute risk: the risk to get an event for the population under study.

Although absolute risks cannot be calculated in a case-control study, an estimate can be given by multiplying the prevalence of the outcome in the general population with the odds ratio found in the case-control study, like presented in the discussion of chapter 4. The prevalence of spina bifida is about 0.5 per 1000 births, the odds ratio of spina bifida among valproic acid exposed pregnancies is 12.7; the estimated absolute risk for spina bifida in case of maternal valproic acid exposure is 0.6%.

This example clarifies that a moderate relative risk for a specific malformation, does not necessary coincides a high absolute risk. In particular, for specific malformations these absolute risks are generally small.

Conclusion & future implications

In this thesis the utilization of antiepileptic drugs in pregnancy is estimated for three European countries showing major differences between these regions. This reflects the importance of performing this type of utilization studies as the treatment practice varies between regions. If the use of antiepileptic drugs in the general pregnant population is known, it might be easier to estimate risks for congenital malformations of (the second generation) antiepileptic drugs. The prevalence found among the general pregnant population can give an estimate of what prevalence to expect within EUROCAT. This may help to finally improve the management of epilepsy around pregnancy. Although changing daily practice is known to be hard [11,13].

The studies presented in this thesis are the first pharmacoepidemiological studies performed with the international EUROCAT congenital malformation registries network. The EUROCAT network demonstrated to be a capable source to perform risk assessment studies for drugs that are chronically used. Due to the large population-based regions covered, studies looking at associations between specific drugs and specific malformations can be performed. In particular, the dataset is suitable to test indications identified in other sources (e.g. literature) and to perform direct comparisons between individual drugs. As non-malformed controls are not (yet) available, all analyses are performed relative to other malformations. This is a point that could be improved in future as well as the drug exposure information. Improvement could be achieved by linkage with sources that contain maternal prescription histories and with sources providing information on non-malformed pregnancy outcomes. These two important topics will be explored in EUROmediCAT within an EU Framework 7 funding that started March 2011.

The three case-control studies as presented in part II of this thesis increase the available evidence on safety of the three most often used antiepileptic drugs during pregnancy (in most countries). This information can be used to update or create treatment guidelines for women requiring antiepileptic drugs with childbearing potential.

This thesis also describes results from a health-economic analysis. Such analyses are not common in the field of teratology although it might get more attention in the near future. Due to the ageing of most populations in the western world and the health costs related to this ageing process in the society, it will become even more important that the offspring is healthy. Therefore this type of analyses might help to investigate the best treatment options; not only for the mother but also for the unborn child.

It is easy to conclude from this thesis that women requiring antiepileptic drugs having a child wish are in an awkward position. They need to use a class of drugs, for which drugs are proven not to be safe in pregnancy or for which no sufficient evidence is available to assume that these agents are safe during pregnancy. The second generation antiepileptic drugs are assumed to be potentially safer, but there are hardly any powered published studies available to confirm this. Altogether, it seems even more complicated due to the fact that there is not a very clear population-based picture of the use of specific new antiepileptic drugs in the general pregnant population. In particular, both the prevalence and the use of the specific types of drugs vary between countries.

However, we should keep in mind that despite the increased relative risk for malformations and the advice to try to avoid valproic acid exposure during pregnancy, still the majority of all babies with intra-uterine exposure to valproic acid monotherapy are born without major malformations. The best treatment option can only be made on an individual tailor-made basis. Hopefully, in the near future there will be a very effective 'broad spectrum' antiepileptic drug that turns out to be safe for the unborn child.

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SUMMARY

Teratogenicity of drugs is a highly relevant issue for the majority of women with a child wish. In the Netherlands, almost 80% of all pregnant women received at least one prescription for a drug during pregnancy (chapter 1). Therefore, it is important that women try to plan their pregnancy and discus with their health care provider if they need (to continue) the drug for their condition and if so, what would be the best treatment option considering their situation before pregnancy.

In case of antiepileptic drugs, depending on therapy indication, most women do need to continue their drug use during pregnancy. Four to five per 1000 women receive at least one prescription for antiepileptic drugs during pregnancy (chapter 2). The prescribed type of antiepileptic drugs to women in the general pregnant population varies between countries. The most frequently prescribed antiepileptic drugs in France, Italy and Netherlands were carbamazepine, lamotrigine, phenobarbital and valproic acid (alphabetical order).

Antiepileptic drugs can be split into first and second generation drugs. First generation antiepileptic drugs are all antiepileptic drugs that were introduced on the market before the nineties and second generation agents are those approved since the nineties. Lamotrigine is the most often used second generation antiepileptic drug and is the drug with most information available about the use around pregnancy. Combining the 2,675 lamotrigine monotherapy exposed pregnancy outcomes described within all published prospective cohort studies, gives a general malformation rate of 3.0% [2.3-3.6%] (including possible overlap between some cohorts).

However in 2006 an FDA warning was issued based on a conference abstract presenting a 24-times increased risk for isolated orofacial clefts and 32-times for cleft palate in specific with first trimester lamotrigine use. The EUROCAT network tested the indication for an elevated risk for isolated orofacial clefts using a study population covering about four million births including almost hundred thousand pregnancy outcomes with a major congenital malformation. With the data included no evidence was found for an increased risk for isolated orofacial clefts (0.80 [0.11-2.85]) or isolated cleft palate in specific (1.01 [0.03-5.57]) for lamotrigine monotherapy exposure in the first trimester of pregnancy, relative to other malformations (chapter 3).

Explorative analyses for lamotrigine showed an indication for club foot, which needs further investigation although the drug seems to be relatively safe in pregnancy. In particular, both alternatives valproic acid and carbamazepine are associated with spina bifida and valproic acid is also associated with several other specific malformations (chapter 4 en 5). Spina

bifida is generally considered to be a more severe malformation than a cleft (or a club foot). The risks for specific malformations associated with other antiepileptic drugs are generally unknown.

As there are no save antiepileptic drug alternatives for use during pregnancy, it is very important in which way study results and conclusions based on generally small studies are presented, interpreted and communicated. This could help in preventing unnecessary doubts and fears of patients and health care professionals. It is important to publish all available relevant information, although unconfirmed indications should be placed in context and tested/ confirmed as soon as possible.

Another way to investigate the effects and impact of teratology is to express prevented malformations associated with the choice of a specific drug in terms of money. A cost utility analysis was performed to estimate the differences in costs and health gains if all pregnant women that require antiepileptic drugs would take carbamazepine, lamotrigine or valproic acid (chapter 7). Carbamazepine is not a first choice option for all types of epilepsy; however, if suitable this drug could be considered as a good treatment option as there is a lot of experience with this drug. Furthermore, it seems that carbamazepine is relatively safe in terms of teratogenicity level and the drug is cheap. From a health economic point of view valproic acid would not be considered as a first choice treatment option if carbamazepine is indicated as possible treatment too, due to dominance. Lamotrigine seems to result in a higher quality of life among the offspring, but this drug is more expensive.

Regardless the methods used for exploration and investigation of the risks and consequences of malformations associated with antiepileptic drugs, the choice for the best treatment for a woman can only be made on an individual basis.

In this thesis, only major congenital malformations are taken into account. In daily practice also risks for minor malformations and behavioral effects, which are possibly more common than major malformations, influence the therapy choice.

For women using antiepileptic drugs, it is recommendable to have a preconception discussion with the neurologist. Next to the antiepileptic drug treatment, it is important to recommend folic acid use from at least 4 weeks before conception till 8 weeks in pregnancy, although no conclusive evidence exists for the most effective dose of folic acid among women using valproic acid. In this thesis, no evidence was found for a protective effect of folic acid for valproic acid exposed pregnancies (OR 1.0 [0.1-7.6]) (chapter 6). As the prevalence of spina bifida is 13-times increased among valproic acid exposed pregnancies it is important to investigate further the mechanisms of action on the spine of both folic acid and valproic acid.

Within the EUROCAT network, information is available for live born, still born and terminated (after prenatal diagnosis) pregnancy outcomes with

major malformations. In case-control studies, we use malformed controls not associated with the exposure under study. Non-malformed control groups can be very valuable, as these groups offer the opportunity to calculate the risks relative to the risk in the general population. This effect-size is easier to interpret. However, not all non-malformed control groups are appropriate. As long as non-malformed outcomes are not registered, it is valuable to perform population-based drug utilization studies in the EUROCAT region. These non-malformed controls or these utilization studies can provide an estimate of the prevalence of exposure to specific antiepileptic drugs in the general pregnant population and will help to estimate the frequencies you can expect within EUROCAT.

For the choice of 'our' control group it is more important that exposure to drugs is representative than the fact that the control group consists of non-malformed pregnancy outcomes. Especially, because using malformed controls can help to reduce recall bias. Ideally, one would separately use a non-malformed, a chromosomal and a non-chromosomal malformed control group which are all collected in the same population-based system.

Conclusion & future implications

The studies presented in this thesis are the first pharmacoepidemiological studies performed using the international EUROCAT congenital malformation registries network. The EUROCAT network demonstrated to be a capable source to perform risk assessment studies for drugs that are chronically used. Due to the large population-based regions covered, studies looking at associations between specific (antiepileptic) drugs and specific malformations can be performed.

The three case-control studies as presented in part II of this thesis increase the available evidence on safety of the three most often used antiepileptic drugs during pregnancy (in most countries). This information can be used to update or create treatment guidelines for women requiring antiepileptic drugs with childbearing potential. This thesis also describes results from a health-economic analysis. Such analyses are not common in the field of teratology but may possibly receive more attention in the near future for investigation of the best treatment options; not only for the mother but also for the unborn child.

It is easy to conclude from this thesis that women requiring antiepileptic drugs who are having a child wish are in an awkward position. They need to use a class of drugs, for which drugs are proven not to be safe in pregnancy or for which no sufficient evidence is available to assume that these agents are safe during pregnancy. In particular, both the prevalence and the use of the specific types of drugs vary between countries, although the available teratogenic information is comparable between countries.

However, we should keep in mind that despite the increased relative risk for malformations and the advice to try to avoid valproic acid exposure

during pregnancy, still the majority of all babies with intra-uterine exposure to valproic acid monotherapy are born without major malformations. The best treatment option can only be made on an individual tailor-made basis. Hopefully, in the near future there will be a very effective 'broad spectrum' antiepileptic drug that turns out to be safe for the unborn child.

SAMENVATTING

De teratogeniteit van geneesmiddelen is zeer relevant voor het merendeel van de vrouwen met een kinderwens. In Nederland ontvangt bijna 80% van de vrouwen minimaal een receptgeneesmiddel via de apotheek tijdens de zwangerschap. Het is daarom belangrijk dat vrouwen hun zwangerschap plannen en overleggen met hun zorgverleners of zij in hun specifieke situatie een middel moeten (door)gebruiken en zo ja, welk middel dan de beste optie is.

De meeste vrouwen die anti-epileptica gebruiken, moeten (afhankelijk van de indicatie) deze middelen blijven gebruiken tijdens een eventuele zwangerschap. Tijdens de zwangerschap halen vier a vijf op de duizend vrouwen ten minste een anti-epilepticum bij de apotheek. De voorgeschreven typen anti-epileptica verschillen tussen landen, maar de meest voorgeschreven middelen in Frankrijk, Italie en Nederland zijn carbamazepine, fenobarbital, lamotrigine en valproinezuur (alfabetische volgorde).

Anti-epileptica kunnen worden opgesplitst in eerste en tweede generatie middelen. De eerste generatie middelen zijn geregistreerd voor 1990 en de tweede generatie anti-epileptica zijn geregistreerd sinds 1990. Lamotrigine is het meest gebruikte tweede generatie middel en hiervan is dan ook de meeste informatie beschikbaar over het gebruik rondom de zwangerschap. Als de 2675 eerste trimester lamotrigine monotherapie blootgestelde zwangerschapsuitkomsten die zijn beschreven in gepubliceerde prospectieve cohort studies worden gecombineerd, levert dit een risico op aangeboren afwijkingen van 3.0% [2.3-3.6%] (overlap mogelijk tussen sommige cohorten). Ondanks dat het algemene risico niet is verhoogd, heeft de FDA in 2006 een waarschuwing afgegeven van een 24 keer verhoogd risico op orofacial clefts. Meer specifiek betekent dit een 32 keer verhoogd risico voor cleft palate bij maternaal lamotrigine gebruik tijdens het eerste trimester van de zwangerschap. Dit signaal is getest met het EUROCAT netwerk in een 'population-based' case-controle onderzoek. De studiepopulatie omvatte bijna vier miljoen geboortes en bijna honderdduizend zwangerschapsuitkomsten met aangeboren afwijkingen. Op basis van de geïncludeerde data is geen bewijs gevonden voor een verhoogd risico op orofacial clefts (OR 0.80 [0.11-2.85]) of meer specifiek geïsoleerde cleft palate (OR 1.01 [0.03-5.57]) bij lamotrigine monotherapie gebruik tijdens het eerste trimester van de zwangerschap, vergeleken met andere aangeboren afwijkingen.

Signaalgenererende analyses gaven een indicatie voor een verhoogd risico op een klompvoet. Dit signaal moet verder uitgezocht worden. Al met al, lijkt lamotrigine relatief veilig gebruikt te kunnen worden tijdens de zwangerschap als men kijkt naar het risico op aangeboren afwijkingen. Zeker gezien de twee

meest gebruikte alternatieven: carbamazepine en valproïnezuur, beide zijn geassocieerd met een verhoogd risico op spina bifida bij het nageslacht en valpoïnezuur daarnaast ook met andere specifieke aangeboren afwijkingen is geassocieerd.

Aangezien er geen anti-epileptica zijn waarvan vast staat dat ze veilig gebruikt kunnen worden tijdens de zwangerschap is het erg belangrijk hoe studieresultaten en conclusies, meestal gebaseerd op kleine studies, worden gepresenteerd, geïnterpreteerd en gecommuniceerd. Bovenal is het van belang dat alle beschikbare informatie wordt gepubliceerd, in specifieke context wordt geïnterpreteerd en dat nieuwe signalen zo snel mogelijk worden getest in andere studiepopulaties. Accurate informatie is belangrijk voor patiënten en behandelaren om (onnodige) twijfel en bezorgdheid te verminderen.

Een andere methode om het effect en de impact van teratogeniteit te onderzoeken is het in geld uitdrukken van aangeboren afwijkingen die worden voorkomen als er een ander middel wordt gekozen. De verschillen in kosten en gezondheidswinst zijn geschat voor de situaties dat alle zwangere vrouwen die anti-epileptica nodig hebben carbamazepine, lamotrigine of valproïnezuur zouden slikken. In situaties waar carbamazepine geïndiceerd is lijkt dit een middel om in overweging te nemen gezien de ruime ervaring met dit middel, de relatieve veiligheid als het gaat om teratogeniteit en de lage prijs. Anderzijds zou valproïnezuur vanuit een gezondheidseconomisch uitgangspunt niet als een eerste keus behandeling worden gezien als carbamazepine ook geïndiceerd is in verband met dominantie: carbamazepine is minder teratogeen en kost minder dan valproïnezuur. Lamotrigine ten slotte, lijkt te resulteren in een hogere kwaliteit van leven in het nageslacht, maar het middel is ook duurder.

Ongeacht de methode die wordt gebruikt om de risico's en consequenties in kaart te brengen voor aangeboren afwijkingen geassocieerd met anti-epileptica, kan het beste middel tijdens de zwangerschap alleen per individu worden bepaald. Resultaten zijn gebaseerd op populatieniveau, niet op het niveau van het individu.

De focus in dit proefschrift is gericht op ernstige aangeboren afwijkingen. In de dagelijkse praktijk zijn ook de risico's op minder ernstige aangeboren afwijkingen en ontwikkelingseffecten, die wellicht frequenter voorkomen, van belang voor de uiteindelijke therapiekeuze.

Voor vrouwen die anti-epileptica nodig hebben is het sterk aan te bevelen om ruim voor conceptie een consult te hebben met de neuroloog om daarin hun kinderwens kenbaar te maken en afspraken te maken over het handhaven of veranderen van de huidige therapie. Naast de behandeling met anti-epileptica is het belangrijk dat het gebruik van foliumzuur van minimaal 4 weken voor

conceptie tot en met 8 weken erna wordt geadviseerd. Er is discussie over de meest effectieve dosering van foliumzuur voor vrouwen die anti-epileptica gebruiken. Echter, in een case controle studie in dit proefschrift is geen beschermend effect gevonden van foliumzuur gebruik in valproïnezuur blootgestelde zwangerschappen (OR 1.0 [0.1-7.6]). Aangezien de prevalentie van spina bifida dertien keer verhoogd is onder zwangerschappen blootgesteld aan valproïnezuur is het zeer belangrijk dat de werkingsmechanismen van zowel foliumzuur als valproïnezuur op de neuraalbuis verder worden onderzocht.

In het EUROCAT netwerk neemt in de recentere jaren het aandeel zwangerschapsuitkomsten met aangeboren afwijkingen toe die zijn blootgesteld aan tweede generatie anti-epileptica. Wel blijven de absolute aantallen per tweede generatie middel klein. Mogelijke redenen hiervoor zijn voorkeur voor anti-epileptica waarmee meer ervaring is of lagere teratogeniteit van de tweede generatie anti-epileptica. Om een goed overzicht te hebben van maternaal anti-epileptica gebruik in de algemene zwangere populatie (en niet alleen van zwangerschapsuitkomsten met aangeboren afwijkingen) is het belangrijk om zwangerschappen zonder aangeboren afwijkingen te includeren in EUROCAT. Zolang alleen zwangerschappen met aangeboren afwijkingen zijn geregistreerd op een systematische 'population-based' manier in EUROCAT is het zeer waardevol om 'population-based' geneesmiddel gebruikersstudies naar anti-epileptica te doen in de EUROCAT regio. Deze controles zonder aangeboren afwijkingen of deze gebruikersstudies geven een beeld van de prevalentie van specifieke anti-epileptica blootstelling in de algemene zwangere populatie en helpen te schatten welke frequenties verwacht kunnen worden in EUROCAT als het middel niet geassocieerd zou zijn met aangeboren afwijkingen. Binnen het EUROCAT netwerk is informatie beschikbaar over levend geborenen, dood geborenen en afgebroken zwangerschappen (na een prenatale diagnose) met aangeboren afwijkingen. In case controle studies met EUROCAT worden controles met aangeboren afwijkingen gebruikt die niet zijn geassocieerd met de blootstelling die wordt onderzocht. Controle groepen zonder aangeboren afwijkingen kunnen erg waardevol zijn, omdat hiermee het risico kan worden berekend ten opzichte van de algemene populatie zonder aangeboren afwijkingen. Deze uitkomstmaat is makkelijker te interpreteren dan een berekening ten opzichte van zwangerschapsuitkomsten met andere aangeboren afwijkingen. Toch zijn niet alle controle groepen zonder aangeboren afwijkingen geschikt.

Het is voor de keuze van de controle groep belangrijker dat de blootstelling aan geneesmiddelen representatief is dan dat de controle groep bestaat uit zwangerschapsuitkomsten zonder aangeboren afwijkingen (binnen farmaco-epidemiologie). Vooral omdat het gebruik van controles met aangeboren afwijkingen voordelen kan hebben: ze zijn vaak op dezelfde manier verzameld

en ze kunnen helpen om 'recall bias' te verminderen. In het ideale geval worden er drie controle groepen gebruikt: een zonder aangeboren afwijkingen, een met chromosomale afwijkingen en een met non-chromosomale aangeboren afwijkingen, die alle drie zijn verzameld in hetzelfde 'population-based' systeem.

Conlusie & toekomstperspectieven

De studies in dit proefschrift zijn de eerste farmaco-epidemiologische studies uitgevoerd met het internationale EUROCAT netwerk voor registraties van aangeboren afwijkingen. Het EUROCAT netwerk heeft bewezen geschikt te zijn om 'risk-assessment' studies uit te voeren voor geneesmiddelen die chronisch worden gebruikt. Door de grote 'population-based' dataset is het mogelijk om associaties te onderzoeken tussen specifieke anti-epileptica en specifieke aangeboren afwijkingen.

De drie case controle studies in deel twee van dit proefschrift vergroten de beschikbare informatie over de veiligheid van de drie meest gebruikte anti-epileptica tijdens de zwangerschap (in de meeste landen). Deze nieuwe informatie kan worden gebruikt om behandelrichtlijnen voor vrouwen in de vruchtbare leeftijd die anti-epileptica nodig hebben op te stellen of te vernieuwen. Dit proefschrift beschrijft verder de resultaten van een gezondheids-economische analyse. Dergelijke analyses zijn niet gebruikelijk binnen het onderzoeksgebied van de teratologie, maar wellicht komt hiervoor meer aandacht in de toekomst door de vergrijzing en het daaruit voortkomende groeiende belang van een optimale verdeling van het gezondheidszorgbudget. Economische analyses kunnen wellicht bijdragen aan de inventarisatie van de beste behandeloptie, niet alleen voor de vrouw zelf, maar ook voor het ongeboren kind.

Het is gemakkelijk om op basis van dit proefschrift te concluderen dat vrouwen met een kinderwens die anti-epileptica nodig hebben in een lastige situatie zitten. Ze hebben een groep van geneesmiddelen nodig waarvan bewezen is dat ze niet veilig zijn of waarvan de veiligheid tijdens de zwangerschap onbekend is. Bovendien variëren zowel de prevalentie als de gebruikte specifieke middelen in verschillende Europese landen. Dit terwijl er geen reden is om te veronderstellen dat het teratogene risico anders is in Frankrijk dan in Nederland en terwijl de richtlijnen worden gebaseerd op dezelfde wereldwijd beschikbare informatie.

Uiteindelijk is het belangrijk om in het achterhoofd te houden dat ondanks het verhoogde relatieve risico op aangeboren afwijkingen en het advies om valproïnezuur gebruik te vermijden tijdens de zwangerschap, het merendeel van de kinderen die zijn blootgesteld aan valproïnezuur monotherapie, wordt geboren zonder ernstige aangeboren afwijkingen. De beste behandeling kan alleen per situatie worden bepaald; hopelijk komt er in de toekomst een effectief 'breed spectrum' anti-epilepticum dat veilig blijkt te zijn voor het ongeboren kind.)

DANKWOORD

Met de afronding van mijn proefschrift is er een eind gekomen aan mijn tijd op de Rijksuniversiteit Groningen. Een zeer leerzame en leuke periode! Zowel tijdens mijn studietijd als tijdens mijn promotietraject heb ik veel mensen ontmoet waarvan ik veel heb geleerd, op allerlei gebied. Graag wil ik dan ook op deze plek van de gelegenheid gebruik maken om de mensen die ik door mijn werk op de Rijksuniversiteit Groningen heb ontmoet te bedanken voor hetgeen ze voor mij hebben betekend of nog steeds betekenen.

Toen ik voor het schrijven van dit dankwoord een lijstje maakte met namen van mensen die ik graag persoonlijk wil bedanken, ontdekte ik dat het niet zwart-wit is wie er wel en niet op komt. Ook realiseerde ik mij direct dat het onvermijdelijk is dat ik na het drukken ontdek dat ik leuke anekdotes of zelfs personen die mij hebben geholpen vergeten ben in dit dankwoord. Als je na het lezen van de rest van het dankwoord te vergeefs naar jouw naam hebt gezocht behoor je misschien tot deze categorie; in dat geval mijn excuses en alsnog bedankt!

Boven aan mijn lijstje staan met stip mijn twee promotoren: Lolkje en Helen.

Lolkje, in 2004 klopte ik voor het eerst aan jouw deur voor mijn bachelorproject en vanaf dat moment was ik veel op de afdeling te vinden voor onderzoek en vakken. Vooral het uitwerken van een onderzoeksvraag tot een werkzame design vond ik erg leuk. Dit heeft in al die jaren samen met jou frisse kijk en enthousiasme geleid tot leuke studies. Dankjewel voor je begeleiding. Tijdens mijn masterproject met EUROCAT en in het begin van mijn promotie traject zijn we samen vaak naar Belfast gevlogen. Ik heb deze reisjes altijd erg bijzonder gevonden: zeer leerzaam, efficient en interessant, maar ook erg vermoeiend. Tijdens deze reisjes bezochten we mijn tweede promotor Helen Dolk aan de University of Uster. Helen I learnt a lot from you, especially your cautious way of working and your last minute inspiration improved my research. Thank you! I will never forget the last days of July 2007, just before the deadline of the original lamotrigine study. Our working days were inspiring and very long, but we made it! I very much enjoyed our sightseeing trip on the first of August.

Graag wil ik ook de leden van de leescommissie bedanken. Dear professor Irene van Langen, associate professor Sonia Hernandez-Diaz and professor Dick Lindhout, I would like to thank you for your time spent to read and judge my thesis.

I would like to thank all my co-authors. Without you it would not have been possible to perform the studies. Especially, I would like to thank all people from the local EUROCAT registries for their collaboration, inspiration and trust. Dear Vera and Guy from Antwerp; Isabel and Larraitz from Basque Country; Mary and Maria from Cork & Kerry; Ingeborg and Ljubica from Croatia; Elisa, Amanda and Francesca from Emilia Romagna; Yves, Christine and Myriam from Hainaut, Annette and Awi from Mainz, Miriam from Malta; Marian, Hermien and Linda from Netherlands, Lorentz, Stein Emil, Jon Gunnar and Kari from Norway; Ester from Odense; Catherine, Babak and Nathalie from Paris; Anna and Jan from Wielkopolska and Poland; Simone and Anke from Saxony Anhalt; Bérénice from Strasbourg; Fabrizio and Anna from Tuscany; Marie-Claude from Vaud and David from Wales...Thank you! Although I missed the last two, I really enjoyed the interesting and 'gezellige' EUROCAT meetings. Those meetings were like family days!

I also would like to thank Maria, Barbara and Ruth from the Central Registry. Thank you for your support and help. Maria, thank you for all the time you put in the creation of the datasets. I enjoyed working with you. Ester, Ingeborg, Elisa and Diana, I learnt so much from you about malformations, ICD-classification and syndromes. Thank you, your experience was extremely valuable! Joan, thank you for your help and support in the statistics on small and large numbers!

Beste Marian, graag wil ik je bedanken dat ik in 2008 1 dag per week in de Nederlandse EUROCAT registratie kon werken. Dit was zeer leerzaam. Daarnaast hebben we een aantal leuke projecten samen gedaan (chapter 1 en 6).

Graag wil ik de door mij begeleidde studenten bedanken. Ik vind het werken met studenten altijd erg inspirerend en het houd je scherp. Bedankt.

Graag wil ik alle medewerkers van de afdeling FE² en FTFPZ bedanken. Een paar mensen wil ik graag nog even apart benoemen. Maarten, je hebt me bij een aantal farmacoeconomische projecten begeleid. Ook al had ik in eerste instantie een puur epidemiologisch project, jouw vakgebied interesseert me sterk. Ook qua persoonlijkheid viel er veel te leren; in sommige opzichten zijn we denk ik echt tegenpolen en vullen we elkaar aan. Bedankt voor je begeleiding en warme interesse.

Natuurlijk wil ik ook graag mijn kamergenoten bedanken voor de gezelligheid en goede discussies. Tijdens het begin van mijn promotie aan de Bloemsingel 1 mocht ik een zeer ruime kamer delen met Silvia. We begonnen onze communicatie in het Engels maar als 1 van ons niet op een woord kon komen kwam je altijd feilloos met het Nederlandse woord. Naar verloop van tijd zijn we dan ook geheel overgegaan op het Nederlands. Helaas ben je door de scheiding van de afdelingen naar een andere kamer verhuisd en hebben alleen nog even samengewerkt aan jouw case-controle studie. Ik wens je veel succes bij afronding van je proefschrift.

Na de kamer herindeling mocht ik mijn kamer delen met Hao. Every time I here you talking Chinese I start smiling. I cannot understand a single word, but it always sounds so happy and funny. I will never forget the day that Lolkje entered our room with an article, which she co-authored, translated into Chinese. Lolkje thought that it was a summary as it was much shorter than the original paper. She looked so surprised when you had a look at the symbols and started translating the paper. You will take over the lamotrigine follow-up project next to your EUROmediCAT work. Since I started to show you the ropes within the EUROCAT dataset, I more and more realized how interesting and special the EUROCAT network is. I wish you all the best.

Ineke als externe aio was je vaak tijdens mijn vrije dag op de universiteit. Wel hebben wij samen een reis naar Boston gemaakt voor de 'Human Teratogens course' aan de Harvard Medical School. Een mooie ervaring. Ik wens je veel succes met de afronding van je proefschrift.

Priscilla, samen waren wij de twee parttime werkende moeders bezig met hun promotietraject. Naast inhoudelijke discussies konden we gezellig kletsen over het wel en wee van onze gezinnetjes. Er zit heel wat werk van jou in het 'Gezond Zwanger' project. Helaas bleek na evaluatie (general discussion) dat de geïncludeerde zwangerschappen niet representatief waren voor de algemene zwangere populatie in Noord Nederland. Gelukkig, zijn er volop nieuwe plannen! Veel succes en plezier met je promotie traject

Graag wil ik ook de heren van de IADB.nl bedanken voor het feit dat ze elke |keer over hun hart streken en de door mij uitgedachte platte tabel produceerden. Ook zullen jullie af en toe wel hard hebben moeten lachen als ik weer eens bij jullie binnen liep voor advies bij rare computer dingen. Dankjewel dat jullie altijd voor mij klaar stonden!

Een promotietraject blijft voor familie en vrienden soms maar een lastig iets. Is het nou werk of opleiding en hoe noem je die scriptie ook al weer waar je alles in bundelt aan het einde. Whatever, ... Bedankt voor jullie eeuwige interesse en jullie luisterend oor als het niet allemaal liep zoals ik graag zou willen!

Lieve Marlies, ik vind het fijn dat jij mijn paranimf bent. Soms zien we elkaar regelmatig, soms een hele tijd niet. Maar als we bijkletsen is het altijd gezellig en net alsof we elkaar pas nog hebben gezien. Tijdens de studie deden we samen commissiewerk en in onze aio-tijd waren we samen zwanger. Het lijkt mij erg gezellig als jij met je mannen op termijn ook afzakt naar het midden van het land!

Lieve papa & mama, Hermy, William, Anouk & Marloes, Wilma, Mark, Arjen, Anne & Heike, Robert, Ellen & Tom, heit & mem en Johannes, Annie & Anton het onderzoek aan de universiteit moet voor jullie vaak behoorlijk abstract zijn geweest, toch hebben jullie mij altijd gesteund en gestimuleerd.

Dankjewel! Paps en mams, jullie kleine meisje was al 'lang' (thuis), maar ondertussen wordt ze ook een beetje groot! Door jullie positieve, inspirerende en bezige voorbeeld heb ik naast mijn studie en promotietraject vele leuke ervaringen opgedaan. Ik hoop dat ik straks voor Coen ook zo'n inspiratiebron kan zijn!

Lieve Cornelis, ruim twee jaar geleden ging jij mij voor en mocht ik aan je zijde staan als paranimf. Nu draaien we de rollen om! De afgelopen jaren hebben we samen heel wat mogen meemaken, gelukkig vooral mooie dingen. Ik wil je graag bedanken, omdat je er altijd voor me bent, je dingen weet te relativeren als mijn relativeringsvermogen me even in de steek laat en me helpt om dingen voor elkaar te krijgen. Vooral in de periode dat jij al bij GSK werkte en we nog in Haren woonden realiseerde ik mij hoe gelukkig ik ben met jouw aanwezigheid en jouw liefde in mijn leven. Het gaf de weekenden een extra dimensie, straks ook door de week! Zeker het afgelopen jaar, samen met onze trots!

Lieve Coen, ook al snap je er nog helemaal niets van en heb je het liefst dat mama niet werkt en gewoon de hele dag bij jou is. Door het afronden van dit boekje word je mama doctor, maar je mag nooit vergeten dat mama haar mooiste titel heeft gekregen door jouw geboorte!

Lieve mannen, ik heb zin in de toekomst samen met jullie!

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CURRICULUM VITAE

Janneke Boersma-Jentink was born in Balkbrug on November 30 1983. After finishing secondary school at the Agnieten College, location Meander in Zwolle, she started her Pharmacy study at the University of Groningen in 2002. Janneke obtained her master degree in Medical Pharmaceutical Sciences with the study direction Management & Policy, cum laude, in 2007.

After graduation Janneke continued her research focused on drug use around pregnancy during a PhD-trajectory at the University of Groningen at the department of PharmacoEpidemiology and PharmacoEconomics. Here she performed pharmacoepidemiological and pharmacoeconomic research on antiepileptic drug exposure in the first trimester of pregnancy and the risk for congenital malformations in the offspring.

Next to this, Janneke worked for one year, one day a week (2008) at the Dutch EUROCAT registry of congenital malformations, for two years (30%) as an academic teacher at the University of Groningen (2009-2010) and for two years as a health economic assistant at HECTA B.V. (2009-2010).

In 2010 Janneke received the Alessandra Lisi Memorial Prize and the SHARE Top publication award in 2010 and 2011.

Currently, Janneke is working as a Drug Safety Specialist for Celgene in Utrecht. Janneke lives together with her husband Cornelis and son Coen.