Maternal epilepsy and pregnancy outcome

A population-based study

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Maternale epilepsie en de pasgeborene
Een populatieonderzoek

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To those not afraid of doubt
To those who wonder why
inexhaustible and at the expense of suffering and dying
To those facing the dilemma of giving or refusing life
this book is dedicated
by a woman
to all women

Oriana Fallaci

Till alla jag älskar

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Chapter 1

Introduction

1 Introduction

The teratogenic effects of thalidomide in the early sixties[1] has marked a period of increasing awareness of the potential dangers of drugs and chemicals to the unborn child. However, despite possible teratogenic effects, offspring of women with epilepsy often are exposed to antiepileptic drugs prenatally. This happens because occurrence of epileptic seizures themselves during pregnancy may pose a considerable risk for mother and child,[2, 3] and so treatment is maintained during pregnancy to control such seizures. The first formal investigations of teratogenicity after the introduction of antiepileptic drugs such as phenobarbital (1912), phenytoin (1938), carbamazepine (1961) and valproate (1964) came from Germany,[4] shortly thereafter followed by reports from England, describing a pattern of major and minor anomalies involving orofacial, cardiovascular, and skeletal systems in children prenatally exposed to antiepileptic drugs.[5, 6] Since then, several studies have addressed the risk of major congenital abnormalities in the offspring of women with epilepsy.[7-12] Most of these studies showed a two- to three fold increased risk of major congenital abnormalities in the offspring associated with antiepileptic drug use during pregnancy. Yet at present, controversy still exists whether this risk is attributable to the teratogenicity of the antiepileptic drug itself, to a genetic predisposition associated with epilepsy,[13] to the occurrence of seizures during pregnancy,[14] or a combination of these.[15]

The risks associated with specific antiepileptic drug regimens have not been clarified. In general, monotherapy is preferred above combination therapies,[16] but safety may differ between antiepileptic drugs in monotherapy. [17, 18] Furthermore, teratogenic risks may be dose-dependent, and the risks of specific major congenital abnormalities may differ between antiepileptic drug regimens. In addition to major congenital abnormalities, minor anomalies, psychomotor development and growth (i.e. weight, length or head circumference) are also important endpoints of teratogenesis. Findings of studies evaluating these outcomes have been contradictory.[19-22]

Although experimental studies with antiepileptic drugs administered to pregnant animals have confirmed the teratogenic potential of most antiepileptic compounds, such results were usually only obtained after human findings indicated teratogenesis. Although experimental studies can be of use in sorting out the contribution of maternal genetic and teratogenic factors, they are difficult to extrapolate to the human situation due to extensive interspecies and interstrain susceptibility, and high frequency of polytherapy in maternal epilepsy.[23,24]

A problem in the clinical interpretation of risk of major congenital abnormalities as found in studies conducted to date is that selection bias may have occurred in a number of the case series studies. Although this problem has been resolved for a large

part in (ongoing) follow-up studies, these latter studies have been small, resulting in a low statistical power and unstable risk estimates. To overcome these problems, two extensive cohort studies described in this thesis were initiated, aiming to quantify the risk of adverse pregnancy outcome associated with maternal epilepsy. The first study is a European collaborative reanalysis of five prospective follow-up studies. The second study is a retrospective population-based follow-up study in the southwestern area of The Netherlands.

In Chapter 2 of this thesis an overview is given of the role of epilepsy in major congenital abnormalities. Chapter 3 summarizes the methods and study design. Chapter 4 describes the results of the European collaborative reanalysis of five follow-up studies from Germany (Berlin and Magdeburg), Finland (Helsinki) and The Netherlands (Rotterdam and the epilepsy institutes). In Chapter 5 the results are presented of the retrospective population-based follow-up study in the southwestern part of The Netherlands. Chapter 5.1 describes the risks of major congenital abnormalities associated with maternal epilepsy and exposure to antiepileptic drugs. Chapter 5.2 deals with the association between specific antiepileptic drug regimens and major congenital abnormalities in the offspring. In Chapter 5.3 the association between antiepileptic drugs and fetal growth and perinatal outcome is described. Finally, in Chapter 5.4 a case-report is presented discussing a possible genetic predisposition to carbamazepine-induced abnormalities in two siblings. Chapter 6 presents a discussion of methodologic issues and findings of the studies in this thesis, as well as the clinical implications of the findings.

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Chapter 2

Maternal epilepsy and major congenital abnormalities: a review

2. Maternal epilepsy and major congenital abnormalities: a review

Introduction

The estimated prevalence of epilepsy lies between four and ten persons per 1000 in the general population.[1] About 25% of these are women in childbearing age.[2] With the elimination of discriminatory legislation, an increase in public tolerance and understanding, and the availability of antiepileptic medication, more women with epilepsy are marrying and raising families. It has been estimated that, yearly, about 0.3%-0.4% of all children are born to mothers with epilepsy.[3]

The attitude towards epilepsy patients has long been one of fear and isolation, and treatments have been available only relatively recently.[4] Potassium bromide, the first antiepileptic drug, used by Sir John Laycock, was actually developed to diminish the sexual drive of epilepsy patients, and not to treat their seizures. It was not until the beginning of this century that antiepileptic drugs such as phenobarbital (1912) and phenytoin (1938) became available for the treatment of epilepsy, and this progress continued with the introduction of less sedative drugs, such as carbamazepine (1961) and valproate (1964). It has long been thought that sufferers from epilepsy should not reproduce, and in many areas of the United States women with epilepsy could compulsorily be sterilized in hospital. In many states it was forbidden for persons with epilepsy to marry (South Carolina Penal Code, 1976). Not until our generation, have people with epilepsy been granted the same rights and privileges as non-epileptics.

The improvement of medical treatment together with public understanding of the disease, have led to wider opportunities for women with epilepsy to marry and have children. This has also brought an increasing awareness of the potential dangers of drugs and chemicals to the unborn child,[5] especially once the teratogenic effects of thalidomide became evident in the early 1960s.[6] The first formal investigations came from Germany,[7] followed shortly thereafter by reports from the UK, describing a pattern of major and minor anomalies involving orofacial, cardiovascular, and skeletal systems in children prenatally exposed to antiepileptic drugs.[8-10]

Besides an increased risk of congenital abnormalities in the offspring of women with epilepsy, there also seems to be an increased risk of pregnancy complications.[11] There is an increased risk of obstetrical complications, such as vaginal haemorrhage, anaemia, hyperemesis gravidarum, pregnancy induced hypertension and preeclampsia, and premature labour.[11-15] A higher frequency of labour induction and artificial labour has been reported;[15] however, others have found that the higher rate of artificial labour could not be explained by a higher frequency of medical indications for such procedures.[16]

About 30% of women with epilepsy will have an increase in seizure frequency

during pregnancy.[17] There are several hypotheses to explain this increase such as hormonal (increase in serum estrogens), metabolic (increased sodium and water retention), psychological (increased stress and anxiety), physiological (sleep deprivation), and pharmacokinetic mechanisms. The last one, a decrease of plasma drug concentration, is probably the most frequent cause.[18, 19] Several mechanisms to explain the decline of antiepileptic drug levels have been proposed, such as intestinal malabsorption,[20] decreased plasma protein binding,[21, 22] reduced concentration of albumin, and increased drug clearance.[23-27] On the other hand, if the albumin concentration and the protein binding decrease, the plasma levels of unbound drug could remain unaltered, which would not necessitate adjustment of the dose if seizure activity does not increase. Also non-compliance could play a role because of concern about the influence of antiepileptic drugs on the child. Because of the high risks associated with convulsions during pregnancy, both for mother and fetus, monthly monitoring of antiepileptic drug levels has been advised.[28] Status epilepticus has a high maternal and perinatal mortality. Of 29 reported cases,[29] nine of the mothers and 14 of the infants died during or shortly after an episode of status epilepticus. Generalized seizures also have other adverse effects on the fetus, such as hypoxia (observed in fetal heart rate),[30] and acidosis.[31, 32] It has been suggested that such seizures cause structural defects when occurring in the first trimester, or mental retardation when occurring in the third trimester of pregnancy.[25] So far, however, no proof for such a causal relation exists, mainly due to lack of a significant proportion of observations of abnormalities associated with generalized maternal seizures during the malformation-specific period of pregnancy. Whether partial seizures can have an effect on the fetus is still unknown.

The high risk of complications with generalized seizures is also one of the reasons why it is usually not wise or possible to discontinue medication during pregnancy. Even if it were possible to ensure a complete seizure-free pregnancy without antiepileptic medication, many women do not consult their doctor until several weeks after conception. The slow dose reduction which is necessary to safely discontinue antiepileptic drugs will not prevent exposure of the embryo to the drug during organogenesis. Furthermore, the risk of a grand mal seizure is increased during labour. Although the absolute frequency of a grand mal seizure during delivery of 1-2% is small, the probability is about nine times higher than on average during pregnancy.[33]

Finally, controversy remains as to whether genetic factors associated with epilepsy itself, maternal seizures, or other complications of pregnancy are responsible for the increased rate of adverse pregnancy outcome, or whether this is exclusively due

to a direct teratogenic effect of the drug. With most cases of developmental and growth abnormalities though, interaction between or addition of genetic and environmental factors plays a significant role.[34, 35] Some investigators believe that antiepileptic drugs only induce congenital abnormalities in the offspring of epileptic mothers who are genetically predisposed.[36] Others believe that the severity of the seizure disorder determines wether a child is born with an abnormality, and not its drug treatment,[37] but this hypothesis has not yet been confirmed or even corroborated by later reports. Most studies clearly have too small a denominator for effective stratification for maternal epilepsy and seizure types, and for family history. The elucidation of genetic factors in epilepsy by molecular genetic methods may help in the future to resolve the contribution of genetic and teratogenic factors in adverse pregnancy outcome.

Epidemiological studies

It remains difficult to determine any single cause, but antiepileptic drugs seem to play an important role in the development of major congenital abnormalities, regardless of confounding factors such as type of epilepsy. Many epidemiologic studies have been and are still being performed, and so far, most of them have shown a two- to threefold increase in risk of congenital abnormalities in the offspring of epileptic mothers using antiepileptic drugs during pregnancy compared with the general population.

Different types of epidemiological studies have been performed over the past few decades, investigating the risks of congenital abnormalities in the offspring of mothers with epilepsy, with or without antiepileptic drug use during pregnancy, and some of them will be discussed here.

Case-control studies

Case-control studies are an efficient way to study rare outcomes, such as congenital abnormalities, since the selection procedure focuses on the outcome in which one is interested, and not on all pregnancies of which the majority will have a normal outcome.[38] Case-control studies also have disadvantages, for example selection bias and the possibility that the data on exposure, which are collected retrospectively, are incomplete and also subject to bias. Most case-control studies, however, have consistently shown a two- to fourfold increase in prevalence of maternal epilepsy among offspring with major congenital abnormalities as compared with prevalence of maternal epilepsy in the general population.[3, 39-42] Not all studies controlled for type of epilepsy or seizures, making it difficult to separate the teratogenic effect of

antiepileptic drugs from a possible predisposition to structural birth defects genetically related to the maternal epilepsy, or from the teratogenic influence of seizures during pregnancy.

In summary, the studies show a four- to 11-fold increased risk of orofacial clefts,[43-46] and a four- to sevenfold increase in risk of congenital heart defects for offspring of mothers with epilepsy,[41, 47] and a causal relationship between valproate use and neural tube defects (odds ratio 21).[3, 48-52] The relation between maternal valproate use and open neural tube defects was subsequently confirmed by a prospective multi-centre cohort study.[53]

Cohort studies

Cohort studies, retrospective as well as prospective, are an accurate means to study relatively rare exposures, such as epilepsy with or without antiepileptic drug use during pregnancy. Ascertainment of the cohort is based on exposure factors, and occurs before or independent of the outcome, in prospective or retrospective designs respectively.[54] The advantage of cohort studies is that they give an estimate of the absolute and relative risks of an exposed versus an unexposed group.
Disadvantages of cohort studies are frequently a lack of sufficient sample size with regard to the outcome of interest, i.e. major congenital abnormalities, and the possibility of confounding by indication. In addition, in retrospective cohort studies there could be the problem of incomplete data, and in prospective cohort studies loss to follow-up might be a problem.

Several retrospective[10, 55-59] and prospective[40, 53, 60-65] studies have been performed. Although these cohort studies differ in methodology and populations studied, they all show a variably increased prevalence of major congenital abnormalities among the offspring of epileptic women as compared with the offspring of non-epileptic controls.[3] Some of these cohort studies have focused on the differences in risk of major congenital abnormalities between women with epilepsy taking antiepileptic drugs during pregnancy and those not taking antiepileptic drugs.[56, 61, 66, 67]

The studies show a two- to threefold increased risk of major congenital abnormalities in the offspring of women with epilepsy using antiepileptic drugs during pregnancy compared with non-epileptic controls, whereas women with epilepsy without antiepileptic drug use during pregnancy seem to have the same risk as the general population. The last risk estimate may not be completely reliable, since the numbers of untreated women with epilepsy in the studies performed so far were very small, and stratification for type and severity of epilepsy was often not possible. It is yet unclear

whether certain types of epilepsy, independently from the treatment, are associated with a higher risk of major abnormalities than others. Studies with larger numbers of untreated epileptic women are needed to give more insight into this issue.

Malformation patterns associated with antiepileptic drugs in monotherapy

Although the overall relative risk of major congenital abnormalities in the offspring of women with epilepsy using antiepileptic drugs is increased two to three fold compared to the general population, the relative risks of specific major abnormalities associated with specific drugs may be much higher,[68] as is demonstrated by the specific association between valproate use and neural tube defect (see above). In fact, the valproate experience, and to a lesser extent that with carbamazepine, has demonstrated that the teratogenic risk of the different medications may conform to the overall two- to threefold increased risk, but may differ with respect to the pattern and spectrum of the defects.

Hydantoins

Hydantoins in monotherapy have been associated with a pattern of abnormalities, termed the fetal hydantoin syndrome,[69, 70] consisting of prenatal and postnatal growth deficiency, microcephaly and developmental delay, combined with dysmorphic features such as craniofacial abnormalities, especially hypertelorism, and nail and distal phalangeal hypoplasia. In the study by Hanson and Smith,[69] 11% of the children exhibited this pattern of abnormalities, while none of the non-exposed controls did. Major congenital abnormalities associated more often than expected with phenytoin, are facial clefts and congenital heart defects.[46, 47, 71] Other defects reported to be associated with hydantoins are urogenital abnormalities,[72] subcutaneous vascular abnormalities,[73] ocular abnormalities,[74] and various types of mainly embryonic tumours.[75-77] These were predominantly case reports and most of the cases were simultaneously exposed to other antiepileptic drugs during pregnancy. It is therefore uncertain whether hydantoins were (solely) responsible for these abnormalities.

Several studies investigated whether there exists a dose-response relationship for antiepileptic drugs and major or minor abnormalities. Concerning phenytoin, some have found a positive dose-response relation,[18, 78] and some have found no dose-response relationship.[61, 66, 79, 80] Furthermore, with the same daily dose and intake, there is a large inter-individual variation in plasma concentration of antiepileptic drugs, making it very difficult to draw any conclusions from a dose-response relationship, when plasma

levels are not known, and the actual fetal exposure can not be sufficiently quantified. Conversely, when only plasma levels are known, but dosages not, no conclusion can be drawn with regard to dose-response relationship, since plasma levels do not only depend on dose, but also on factors such as co-medication and pharmacogenetics. Relatively few studies though, have assessed maternal antiepileptic drug plasma levels,[18, 81] and the results of the different studies are not consistent.

Barbiturates (phenobarbital and primidone)

Barbiturates in monotherapy have also been associated with congenital heart defects and facial clefts[46, 47, 71] and a specific pattern of minor anomalies and dysmorphic features such as growth deficiency, and craniofacial and/or limb abnormalities.[82, 83] Concerning dose-response relationship and plasma levels of these antiepileptic drugs, again there are studies that found evidence for a positive relation,[18, 66, 78] and studies that did not.[79, 84]

Carbamazepine

Recent studies have shown an association between carbamazepine and congenital abnormalities in the same order of magnitude as for barbiturates and phenytoin, but the types of abnormalities are different. The first neonatal findings documented in association with carbamazepine were abnormal growth parameters such as reduced head circumference, weight and length at birth.[59, 85] Several other studies reported major congenital abnormalities, such as hip-dislocation, inguinal hernia, hypospadias, congenital heart defect and neural tube defects.[81, 86-88] The first suggestion of a possible association between carbamazepine and neural tube defects came from a study in 1984.[52] Subsequently eight cases of spina bifida were observed among 1307 carbamazepine-monotherapy exposed pregnancies in a collection of several cohort studies,[89] giving rise to a two- to tenfold increase in risk, as compared with the general population prevalence of neural tube defects which varies in the corresponding general populations from 0.05 to 0.3%. The risk of spina bifida associated with carbamazepine was recently confirmed in a study, in which nine out of 3635 children of epileptic mothers were born with spina bifida, and of whom six had used carbamazepine during pregnancy.[90] In this Swedish study, most of the infants with spina bifida were identified in the period from 1984 throughout 1986. The most probable reason why no new cases were identified after this period, is the increased use of prenatal diagnosis because of treated maternal epilepsy. Cases of neural tube defects prenatally diagnosed and followed by termination of the pregnancy, if they had occurred, were not

ascertained in this study which used data from a registry of deliveries only.

Even though the studies so far suggest that carbamazepine use in pregnancy increases the risk of spina bifida, due to small numbers of affected children the results are not (yet?) statistically significant. The individual risk of spina bifida for infants exposed to carbamazepine during pregnancy is estimated to be 0.5 - 1%, and prenatal diagnosis has therefore been recommended.[33, 91]

Whether a dose-response relationship for carbamazepine use and congenital abnormalities exists is still a subject of discussion. In the study by Lindhout,[81] pregnancies with abnormal outcome were associated with higher serum levels of carbamazepine. However, these abnormal outcomes could also have been associated with an increased seizure frequency, since serum levels were increased only for those women with an increased seizure frequency, who delivered a child with a malformation.

Valproate

The initial report of a possible teratogenic effect of valproate was published in 1980 by Dalens et al.[92] Shortly afterwards, this was followed by several case reports of infants with congenital abnormalities, such as craniofacial, skeletal, cardiovascular, urogenital, cerebral and open neural tube defects.[48, 93, 94] Valproate exposure was subsequently also associated with a combination of facial dysmorphic patterns, distinct from those described with phenytoin exposure.[95, 96] The reports were followed by cohort studies, evaluating major abnormalities such as hypospadias, umbilical and inguinal hernias, cardiovascular defects, skeletal defects and hip dislocation, indeed showing an increased risk for valproate monotherapy, especially with respect to spina bifida.[79, 97, 98] A multi-centre prospective cohort study demonstrated the prevalence of neural tube defects to be 2.5% in offspring of epileptic mothers using valproate monotherapy in pregnancy, 0.35% in offspring of epileptic mothers using other antiepileptic drugs, and 0% in non-epileptic controls.[53] There have also been report about a relationship between valproate and radial ray aplasia, rib and vertebral anomalies.[81, 96, 99-101]

Valproate is probably the only antiepileptic drug for which a dose-response relationship has been observed rather consistently. A higher daily dose or a higher peak dose seem to increase the risk of major congenital abnormalities, irrespective of seizure frequency during pregnancy.[81, 98, 102, 103]

Ethosuximide

Almost all antiepileptic drugs have been associated with congenital anomalies in children of mothers using these drugs during pregnancy. Regarding ethosuximide, major congenital abnormalities, such as facial clefts, have been associated with this drug, but mainly in combination therapies such as ethosuximide + phenobarbital and ethosuximide + primidone. Neonatal behaviour complications and minor anomalies, though, have been associated also with ethosuximide monotherapy.[104] Furthermore, Nau et al. have investigated the role of various antiepileptic drugs, in monotherapy or combination therapy, in the vitamin A-retinoid metabolism. Several of these drugs, including the combination of valproate with ethosuximide, induced changes in the levels of endogenous retinoid metabolism products. The effect of ethosuximide monotherapy, however, was not studied. With respect to the level of all-trans-retinoic acid, it was only the combination of valproate and ethosuximide that were associated with an increase, and not the combinations of valproate with other drugs but, again, no data on ethosuximide only were presented.[105]

Benzodiazepines

Initial reports on associations between orofacial clefts and benzodiazepines (diazepam)[106-108] were followed later by studies that were not able to confirm such associations.[45, 109, 110] Benzodiazepines are often used as add-on therapy. In a study by Laegreid et al.,[111] the combination of valproate and benzodiazepam was found to be associated in two cases with neural tube defects in combination with more pronounced dysmorphism, compared to children prenatally exposed to valproate monotherapy. The authors interpreted this as an amplifying action of benzodiazepines on valproate teratogenicity.

Dose-response relationship

The establishment of a dose-response relationship between fetal exposure and fetal outcome is one of the basic criteria of teratogenesis according to the principles set by Wilson. These principles include that a teratogenic effect is determined by a) the specific structure of the chemical agent, b) the specific genetically determined sensitivity of the exposed species, c) the specific sensitive period of embryonic and fetal development, and d) the existence of a dose-response relationship.[112]

There are several possibilities for evaluating dose-response relationships in studies of human pregnancy exposures such as to maternal antiepileptic drugs. An optimal study design would include the evaluation of different exposure parameters

such as daily dose as a measure for general exposure, highest dose per administration as a measure for peak exposure and an indirect estimate of peak levels in maternal serum, total and free maternal serum levels of the parent drug as well as of metabolites as an indirect estimate of fetal exposure, and amniotic fluid levels of parent drug and metabolites as a more direct and average estimate of fetal exposure. In the optimal design, these measurements would be made preferably in the sensitive period of embryonic development which, however, varies for the different fetal abnormalities, and would imply frequent sampling of the required body fluids. Such an optimal design is difficult to achieve in clinical practice, and may explain at least some of the inconsistencies between the results of the various studies that have attempted to evaluate dose-response relationships. Indeed, most studies evaluated only one or two of the measures of exposures, only in a minority of pregnancies, and not always in the relevant period of embryonic development. The study by Omtzigt is an example of what might be optimally feasible under these conditions.[65] Total daily dose and dose per administration during late embryonic and early fetal development were analyzed, together with serum and amniotic fluid levels obtained in almost all women at the most feasible time-points in pregnancy, namely at referral for prenatal diagnosis (8-14 weeks) and at the time point of amniocentesis or ultrasound examination (16-20 weeks).

Teratogenic risk of antiepileptic combination therapies

There are indications that the risks of congenital abnormalities are higher, or sometimes lower, for antiepileptic combination therapies, depending on the type of combination. Some studies have used a drug score, combining the number as well as the dose of antiepileptic drugs prescribed, and observed a higher frequency of congenital abnormalities with a higher drug score.[66, 79] This last study did not take into account the highest dose per administration of the individual drugs, which may be an important risk factor in the case of valproate use. Another limitation of the drug score method is that it does not take into account the influence of specific interactions between the different drugs within a combination. Specific associations with major abnormalities were found with the combination of phenobarbital + phenytoin + primidone[78] and carbamazepine + phenobarbital + valproate +/- phenytoin.[113]

The increased risks associated with these antiepileptic drug combinations could possibly be ascribed to interaction between these drugs, causing an increase of potentially teratogenic intermediates, such as epoxide intermediates.[114] Another possible mechanism of teratogenicity of the combination of carbamazepine + phenobarbital +

valproate +/- phenytoin has been ascribed to the induction of hyponatremia, which has been associated with in vitro embryotoxicity of patient sera on rat embryos.[115] So far, there have been no studies of human pregnancies that evaluated the risk of hyponatraemia in carbamazepine and oxcarbazepine-related abnormalities. Recently, the potential significance of as yet unidentified carbamazepine metabolites in drug combinations of carbamazepine with other antiepileptic drugs was established by an animal experimental study, in which pregnant rodents were exposed to carbamazepine in combination with a cytochrome P-450-inducer (phenobarbital) or a cytochrome P-450-inhibitor (stiripentol).[116]

The risk of major congenital abnormalities is not always increased with antiepileptic drug combinations, since the interaction of drugs can also work the other way around. A decrease of the plasma level of a potentially teratogenic parent drug or metabolite can reduce the risks of abnormalities compared with that associated with a drug in monotherapy. An example might be the somewhat lower risk of neural tube defects associated with the drug combination of valproate + phenobarbital, in which case phenobarbital seems to reduce valproate levels by induction of valproate metabolism.[117] Indeed, valproate levels and metabolites in human pregnancies were lower with other antiepileptic drug combinations, but the numbers were too small for meaningful evaluation of pregnancy outcome.[103]

Primary prevention

A significant decrease in the occurrence of neural tube defects was demonstrated among pregnant women, without a prior increased risk for neural tube defects (no previous affected child, negative family history, no maternal diabetes, no antiepileptic drug use), who were pre-conceptionally using a multivitamin preparation with a low-dose of folic acid (0.8 mg/day), compared with women using a preparation of minerals with vitamin C only.[118] Following this study, health authorities from several countries have recommended that all women of childbearing age should be supplemented with low-dose folic acid, via a tablet (current dosage in the Netherlands: 0.5 mg/day), by promotion of a folic acid-rich diet, by food fortification, or a combination of these.

Previously, high-dose folic acid supplementation of 4-5 mg/day was recommended for women in the childbearing age with a recurrence risk of neural tube defects.[119] Although maternal antiepileptic drug use, especially valproate and carbamazepine, has been associated with an increased risk of neural tube defects, and a decreased folic acid level has been associated with any adverse pregnancy outcome, including spontaneous abortions in epileptic women using antiepileptic drugs,[78] it is not

yet clear whether it is indicated or safe to prescribe these dosages to epileptic women using antiepileptic drugs. It should be kept in mind that no convincing evidence has been found for involvement of folic acid-related pathways in antiepileptic drug induced teratogenesis. The antiepileptic drugs which induce the most marked decrease in folic acid levels, phenytoin and phenobarbital, are not as strongly associated with neural tube defects as valproate and carbamazepine, which have less influence on folic acid levels. Decisions concerning treating women with epilepsy using antiepileptic drugs during pregnancy should therefore await clear evidence from animal experiments and double-blind randomized placebo-controlled clinical trials. There does not, however, seem to be any reason for withholding low-dose folic acid supplementation. Higher doses may be needed only if such women exhibit symptomatic folic acid deficiency or if other concurrent risk factors for neural tube defects exist.

Recently, pantothenic acid supplementation proved to decrease substantially valproate teratogenicity in mice, especially with respect to the neural tube, and not with respect to skeletal defects induced by valproate.[120] The authors conducted their study on the basis of the hypothesis that valproate induced side effects may be partly mediated through lowering of levels of coenzyme A,[121] which is synthesized from pantothenic acid in a number of metabolic steps. Indeed, valproate interferes with fatty acid metabolism, and it may well be that pantothenic acid and carnitine, when supplemented, have a beneficial effect on some of the side-effects of valproate. In the current phase of knowledge, however, we should await the results of more extensive (animal) experimental studies, and focus on the evaluation of pantothenic acid content of current food intake and frequently used multivitamin supplementations in relation to pregnancy outcome, before (high dose) pantothenic acid supplementation is clinically tested in the human situation of maternal valproate use.

Secondary prevention or prenatal diagnosis of abnormalities

The risk of spina bifida in offspring of mothers using valproate (1-2%) or carbamazepine (0.5-1%) in pregnancy is in the same order of magnitude as the recurrence risk after a previous child with a neural tube defect and when a sibling of one of the parents has such a defect respectively. Therefore, in many countries amniocentesis is performed in week 16 of pregnancy in order to measure the α-1-fetoprotein (AFP) level in amniotic fluid. This level is increased in most cases of an open neural tube defect.[102] Whether maternal serum AFP screening is a reliable method to detect valproate-induced spina bifida is doubtful.[122]

Another widely used method of prenatal diagnosis of major abnormalities is

structural ultrasound screening, which preferably should be performed between 18 and 20 weeks of pregnancy.[88] Prenatal detection of major abnormalities may help to improve perinatal care, and facilitate the acceptance of such abnormalities for parents. It may also provide parents with the option of terminating the pregnancy in the case of very severe, lethal or non-treatable abnormalities. The limitations of prenatal diagnosis, though, should be made known to parents, since not all defects can be diagnosed prenatally. Furthermore, when a malformation is detected, it is not always possible to give a prognosis, whereas other abnormalities, especially mental deficiency, may not be detected until after birth.

Last but not least, the mental and the physical impact of a late termination of pregnancy after amniocentesis or abdominal ultrasound screening should not be underestimated. Perhaps in the future transvaginal ultrasound screening performed in the first trimester may offer the possibility of earlier pregnancy termination, but emphasis should be placed upon primary rather than secondary prevention.

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Chapter 3

Methods

3. Methods

3.1 Introduction

In clinical practice the increased prevalence of major congenital abnormalities in the offspring of women with epilepsy, who were treated with antiepileptic drugs during pregnancy, is well known. However, results of studies of the role of maternal epilepsy have been controversial with regard to the effects of maternal factors and specific antiepileptic drug regimens. The interpretation of findings of individual studies is hampered by the potential of selection bias as well as the low statistical power of each of the studies.[1-3] The rationale of the studies presented in this thesis was to examine the teratogenic effects of antiepileptic drugs and maternal epilepsy in population-based cohorts with larger numbers of exposed pregnancies. The thesis comprises two studies. The first study is a reanalysis of five prospective studies on the role antiepileptic drugs in pregnancy outcome, conducted in Europe between 1971 and 1990. The second study involves a retrospective population-based follow-up study in the southwestern area of the Netherlands. This chapter gives an outline of the design of the two studies.

3.2 The European collaborative reanalysis

Although a number of prospective studies on antiepileptic drugs and major congenital abnormalities in the offspring have been conducted, the value of these studies has been limited by the low statistical power of the individual studies conducted. To overcome this problem, raw data from five studies were pooled and reanalysed. Studies included were prospective studies conducted in Europe in the period 1971-1990. These studies were selected on the basis of a prospective design and before data were analyzed in detail, in order to exclude selection bias based on the outcome of the studies. One of the studie was conducted in Finland (Helsinki), two were conducted in Germany (Berlin [former West-Berlin] and Magdeburg), and two were conducted in The Netherlands (in the municipality of Rotterdam and the Southwestern Netherlands, and the outpatient clinics of the Dutch Special Centres for Epilepsy).

Description of the individual studies

All studies are prospective follow-up studies of the reproductive outcome of pregnancies with maternal epilepsy. The studies recruited all consecutive pregnant women with epilepsy. Berlin and Magdeburg also included non-epileptic control pregnancies. During the International Epilepsy Symposium in Hamburg (1985) a

collaborative analysis of the data of these centres was suggested and a grant application was approved by the Commission on Epilepsy, Pregnancy and the Child of the International League Against Epilepsy and forwarded to the Klingenstein foundation. The study design and in particular the selection of the exposed and non-exposed pregnancies used in this analysis, is described for each study individually below, ordered alphabetically by city.

Berlin, Germany

This study was conducted in the period between 1979 and 1990.[4] The study comprised 123 mothers with epilepsy. Included were 150 antiepileptic drug-exposed pregnancies. Only patients whose epilepsy diagnosis was confirmed by a neurologist and in whom the first seizure occurred before pregnancy, were included. Of the cohort, 80% was ascertained through 12 obstetric clinics in the area of Berlin and 20% through the Neurology department of the former University Hospital Charlottenburg. Control pregnancies (n=116) were selected through the obstetric clinics, matched for maternal age at delivery, parity, social class, smoking habits and previous abortions.

Helsinki, Finland

The study was conducted between 1976 and 1979[5] and comprised 97 mothers with epilepsy. Included were 106 antiepileptic drug-exposed pregnancies. Only patients whose epilepsy diagnosis was confirmed by a neurologist and in whom the first seizure occurred before pregnancy, were included. All maternity units were asked to refer patients with epilepsy for the study to the Helsinki University City hospital. Data on control pregnancies were not available for this reanalysis.

Magdeburg, Germany

The study was conducted between 1979 and 1987 according to a protocol similar to that of the study preformed in Berlin.[6, 7] There were 32 mothers with epilepsy with 42 antiepileptic drug-exposed pregnancies. The diagnosis of epilepsy was always confirmed by a neurologist. In all patients but four the first seizure occurred before pregnancy. Patients were referred to the coordinating neuro-paediatrician by two obstetric departments. The first delivery after birth of the exposed infant was selected as a control pregnancy (n=42).

Rotterdam, The Netherlands

The study was conducted in the period 1985-1990 and comprised 261 women

with epilepsy.[8-11] These women were consecutively referred to the outpatient clinic for prenatal diagnosis of the University Hospital Rotterdam, because of epilepsy with antiepileptic drug (or without antiepileptic drug) use. Only patients whose epilepsy diagnosis was confirmed by a neurologist were included. Data were available for 305 antiepileptic drug-exposed offspring. Amniocentesis or structural ultrasound, and in most patients both, were performed. Some pregnancies were interrupted because of major congenital abnormalities discovered during prenatal diagnosis. These pregnancies were also included in the study. No control pregnancies were selected.

Institutes of Epilepsy, The Netherlands

This cohort comprised 411 women with epilepsy with a total of 618 consecutive antiepileptic drug treated pregnancies, derived from one of 14 outpatient clinics of the Special Centres for Epilepsy in The Netherlands (Instituut voor Epilepsie bestrijding "Meer en Bosch" - "De Cruquiushoeve", Heemstede; Epilepsiecentrum Kempenhaeghe, Heeze; Dr. Hans Bergerkliniek, Breda), in the period 1972-1990. In these centres, approximately 7% of all patient with epilepsy in the Netherlands are treated. The cohort can be subdivided into three cohorts (A, B, C). The first study (cohort A) was conducted between 1972 and 1979 and comprises 151 antiepileptic drug-exposed pregnancies.[12-14] The second study (cohort B) was conducted between 1980-1985 and comprises 172 antiepileptic drug-exposed pregnancies.[15] The remaining pregnancies (cohort C) were collected between 1985 and 1990 and consist of 295 antiepileptic drug-exposed pregnancies (not published before). The diagnosis of epilepsy was confirmed by a neurologist. No control pregnancies were selected.

Endpoints

The main endpoints for all cohort studies were major congenital abnormalities including body measurements, occurrence of neural tube defects, cleft lip and/or palate, skeletal abnormalities, abdominal defects, genito-urinary defects, cardiac defects and dysmorphic features. A more detailed description of the methods of each individual cohort study, including ascertainment of exposed, selection of controls, matching parameters, etcetera, is provided in Chapter 4.

Strategy of joint reanalysis of the studies

To reanalyse the studies, the raw data of the five studies were centralized at the Department of Epidemiology & Biostatistics of the Erasmus University Medical School, Rotterdam. Included in the studies are a total of 896 women with epilepsy

using antiepileptic drugs and 1221 children born to these subjects and 158 non-epileptic control pregnancies. Of the antiepileptic drug treated women, 328 (36%) had generalized epilepsy, 382 (43%) had partial (localisation related) epilepsy, 28 (3%) had unclassified epilepsy and in 158 (18%) women the type of epilepsy was unknown.

An important issue in the collaborative reanalysis was the comparability of data collection, in particular assessment of major congenital abnormalities in the offspring. In the reanalysis presented in this study, we redefined major congenital abnormalities uniformly in collaboration with the principal investigators of the studies, as an abnormality of an essential embryonal structure, present at birth or discovered during the first three months of age and/or requiring significant therapy before the first year of life. Some examples of major congenital abnormalities under this definitions are: neural tube defects (e.g. spina bifida aperta with/without hydrocephalus), congenital heart defects (e.g. ventricular septal defect), hypospadias, cleft lip and/or palate, pre- and/or post-axial polydactyly, club foot or a congenital hip dysplasia requiring plaster therapy, and inguinal hernia (only when requiring an operation).

The assessment of type of epilepsy and of seizures during pregnancy and especially the first trimester was incomplete, and varied between study groups with respect to assessment procedures and definition. Therefore, adequate and comparable data on seizure frequency were not available for reanalysis.

3.3 The retrospective cohort study

In 1982, Robert and Guibaud, described 12 children born with spina bifida aperta exposed to valproate during pregnancy.[16] Valproate was one of the most recently marketed antiepileptic drugs and, apart from a single case-report,[13] little was known about its safety concerning fetal exposure during pregnancy. Based of this finding,in 1983, the Dutch National Institute of Public Health and the Environment (RIVM) initiated the establishment of an 'interdepartmental' commission, in order to initiate studies in the Netherlands and decide on preventive measures to be taken. Two designs were considered: (1) a case-control study, in which antiepileptic drug exposure was to be compared between children with and without major congenital abnormalities, and (2) a retrospective follow-up study, in which exposed and non-exposed children were followed during pregnancy to assess the risk of major congenital abnormalities. Although the case-control design is generally more powerful for rare diseases, in this specific study both the disease (frequency of major congenital abnormalities in the population is 0.5%) and the exposure (frequency of maternal epilepsy is 0.3 - 0.5%)

are rare. As the case-control design is considered to be more prone to bias, and provides a relative risk estimate only, a follow-up design was chosen. A retrospective cohort study was therefore proposed, covering all pregnancies with antiepileptic drug use during pregnancy in the Netherlands since 1971, the year in which valproate was introduced. Such a study would make it possible to ascertain large numbers of pregnancies needed to be able to compare different antiepileptic drug regimens and to determine the specific risks associated with these drug regimens. Furthermore, the study aimed to take other maternal factors into account, including occurrence of seizures and type of epilepsy. However, it lasted until 1992 before the financial support for this study was obtained trough a grant from the Commissie Landelijk Epilepsie Onderzoek (CLEO) of the National Epilepsy Fund.

Subjects and data collection

The study comprised offspring of women with epilepsy, with or without antiepileptic drug use during pregnancy, born between 1972-1994 in 28 hospital in four provinces of the Netherlands. Using hospital delivery books, hospital delivery registration systems, national delivery registration systems (National Perinatal Data Base (LVR)), outpatient clinics for prenatal diagnosis, and obstetrical history, we aimed at ascertaining all deliveries with maternal epilepsy independent of outcome, including pregnancies terminated after prenatal diagnosis. Dysmature and premature deliveries were included, as well as stillbirths and pregnancies terminated because of severe fetal anomalies diagnosed prenatally. Included in the study are 1348 mothers with epilepsy and 2107 children born to these women, as well as 1955 matched non-epileptic controls and 2000 children born to these women. Control pregnancies were matched to the exposed pregnancies for maternal age (+/- 2 years) and parity, and sex, year of birth and hospital of delivery of the child. The study protocol was approved by the Medical Ethical Committee of Erasmus University.

Data collected from medical records included general characteristics of the mother, information on pregnancy and child, obstetrical history, family history, epilepsy, medication and intoxications. Information on type of epilepsy was retrieved from obstetric or neurologic patient files or from correspondence with treating neurologists. Epilepsy of the mother was classified into generalized, partial or unknown. Information on major congenital abnormalities and perinatal outcome measures was also retrieved from patient files and sometimes completed with information from the paediatrician.

Strategy of analysis

Endpoints of the study were major congenital abnormalities in the offspring, defined as an abnormality of an essential embryonal structure, present at birth or discovered during the first six weeks of life. Examples of major congenital abnormalities according to this definition are: neural tube defects (e.g. spina bifida aperta with/without hydrocephalus), congenital heart defects (e.g. ventricular septal defect), hypospadias, cleft lip and/or palate, pre- and/or post-axial polydactyly, club foot or congenital hip dysplasia requiring plaster therapy or surgery, and inguinal hernia, but only when requiring surgery.

For the studies described in Chapter 5.1 and 5.3 the mothers with epilepsy were divided into five exposure groups. Group I *(first trimester exposure)* includes women using antiepileptic drugs at least during the first trimester of pregnancy and possibly during the second and third trimester (921 women and 1411 children). Group II *(only second/third trimester exposure)* includes women who were only treated with antiepileptic drugs during the second and/or third trimester (79 women and 115 children). Group III *(unknown trimester)* includes women who were using antiepileptic drugs in pregnancy, without documentation in which trimester (54 women and 79 children). Group IV *(non-exposed epileptic)* includes women without antiepileptic drug use throughout pregnancy (244 women and 421 children). For 50 (3.5%) women with epilepsy (81 children) no documentation about antiepileptic drug use during pregnancy could be retrieved and this group was therefore not included in the analyses.

For the study in Chapter 5.2 only the 921 (1411 children) women in group I, who were using antiepileptic drugs at least during the first trimester of pregnancy, were included in the analyses, as this is the embryogenic period.

In Chapter 5.3 endpoints of the study were birth weight, length and head circumference, placental weight, and Apgar scores at one and five minutes.

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Chapter 4

Maternal antiepileptic drug use and major congenital abnormalities: A European collaborative reanalysis

4. Maternal antiepileptic drug use and major congenital abnormalities: A European collaborative reanalysis

Abstract

To quantify the risks of intra-uterine anti-epileptic drug exposure, in monotherapy and polytherapy, a joint European re-analysis, pooling data from five prospective studies with a total of 1379 children, was performed. Data were available for 1221 children exposed to antiepileptic drugs during pregnancy and for 158 children of non-epileptic controls.

Overall, when comparing a subgroup of 192 children exposed to antiepileptic drugs with 158 children of matched non-epileptic controls, there was an increased risk of major congenital abnormalities in children exposed to antiepileptic drugs during pregnancy (relative risk (RR) 2.3; 95% confidence interval (CI): 1.2 - 4.7). A significant increase in risk was found for children exposed intra-uterinely to valproate (RR 4.9, CI: 1.6 - 15.0) or carbamazepine (RR 4.9, CI: 1.3 - 18.0) in monotherapy. When comparing different antiepileptic drug regimens during all 1221 pregnancies, risks of major congenital abnormalities were significantly increased for the combination of phenobarbital and ethosuximide (RR 9.8, CI: 1.4 - 67.3) and the combination of phenytoin, phenobarbital, carbamazepine and valproate (RR 11.0, CI: 2.1 - 57.6). Offspring of mothers using more than 1000 mg valproate/day were at a significantly increased risk of major congenital abnormalities, in particular of neural tube defects, compared to offspring exposed to 600 mg valproate/day or less (RR 6.8, CI: 1.4 - 32.7). No difference in risk of major congenital abnormalities was found between the offspring exposed to 601-1000 mg/day and 600 mg/day or less.

This reanalysis shows that valproate is consistently associated with an increased risk of major congenital abnormalities in the offspring. Although we have pooled the data of five studies, the number of women exposed remains small for a considerable number of drug combinations, leading to unstable risk estimates.

Introduction

Maternal use of antiepileptic drugs during pregnancy has been associated with an increased risk of major congenital abnormalities in the fetus. Yet, in a considerable number of women planning a pregnancy it is not possible to withdraw antiepileptic drugs, because of the risk of epileptic seizures during pregnancy, which are harmful to both mother and child.[1-3] Also, acute withdrawal during early pregnancy is not recommended, because of risk of uncontrolled seizures and status epilepticus.[4-6] Many children of mothers with epilepsy are therefore at a two- to threefold increased risk of

congenital abnormalities compared to the general population[7-14], and an important clinical issue is how to treat women with epilepsy during pregnancy.[15-18]

Many questions concerning risks associated with the specific antiepileptic drugs are unanswered. In the studies conducted to date no specific drug regimen consistently showed a lower risk than the other, suggesting that antiepileptic drug therapy is implicitly related to an increased risk of congenital abnormalities. However, most of these studies comprised a relatively small number of pregnancies.[19-23] This limits the possibilities for evaluation of potential dose-response relationships. Furthermore, differences between studies may occur not only in definitions but also in study procedures. In a collaborative analysis, these factors can be taken into account by increasing the number, application of standardized definitions, and evaluation of effects that are consistent across studies.

Therefore, to quantify the specific risks of antiepileptic drugs in monotherapy and polytherapy, a joint European reanalysis with pooling of data from five prospective studies was performed. The focus of the present study is on pregnancies with maternal epilepsy with antiepileptic drug use. The first aim was to assess the risks of major congenital abnormalities for children exposed in utero to antiepileptic drugs during pregnancy compared to the risk in unexposed children. The second aim was to quantify risks of major congenital abnormalities associated with specific antiepileptic drug regimens during pregnancy by comparing patients with different drug regimens.

Methods

The reanalysis was performed using raw data from five studies conducted in Europe in the period 1971-1990. All of the studies selected were prospective and chosen before their data were analyzed in detail, in order to exclude selection bias based on the outcome of the studies. One of the studies was conducted in Finland (Helsinki), two were conducted in Germany (Berlin [former West-Berlin] and Magdeburg), and two were conducted in The Netherlands (in the municipality of Rotterdam and the Southwestern Netherlands, and the outpatient clinics of the Dutch Special Centres for Epilepsy). Included in the studies are a total of 896 women with epilepsy using antiepileptic drugs and 1221 children born to these subjects and 158 non-epileptic control pregnancies (table 1). Of the antiepileptic drug treated women, 328 (36%) had generalized epilepsy, 382 (43%) had partial (localisation related) epilepsy, 28 (3%) had unclassified epilepsy and in 158 (18%) women the type of epilepsy was unknown. The assessment of seizures during pregnancy and especially the first trimester was incomplete, and varied between study groups with respect to assessment procedures and

definition. Therefore, adequate and comparable data on seizure frequency were not available for reanalysis.

Description of the individual studies

During the workshop on Epilepsy, Pregnancy, and the Child (Berlin, 1981), participating groups compared their prospective study designs and concluded that their studies were adequately comparable and therefore suitable for a collaborative analysis, once each of the individual study results had been published. All these studies are prospective follow-up studies of the reproductive outcome of pregnancies with maternal epilepsy. The studies recruited all consecutive pregnant women with epilepsy. Berlin and Magdeburg also included non-epileptic control pregnancies. During the International Epilepsy Symposium in Hamburg (1985) a collaborative analysis of the data of these centres was agreed upon and a grant application was approved by the International League Against Epilepsy and forwarded to the Klingenstein foundation. The comparability of case-ascertainment and the assessment of major congenital abnormalities in the individual studies was evaluated by visiting the study centres and discussing the study protocol. The study design and in particular the selection of the exposed and non-exposed pregnancies used in this analysis, is described for every study individually below. The studies are ordered alphabetically by city and country.

Berlin, Germany

This study was conducted in the period between 1979 and 1990.[24] The study comprised 123 mothers with epilepsy. Included were 150 antiepileptic drug exposed pregnancies (table 4.1). Only patients whose epilepsy diagnosis was confirmed by a neurologist and in whom the first seizure occurred before pregnancy, were included. Of the cohort, 80% was ascertained through 12 obstetric clinics in the area of Berlin and 20% through the Neurology department of the former University Hospital Charlottenburg. Control pregnancies (n=116) were selected through the obstetric clinics, matched for maternal age at delivery, parity, social class, smoking habits and previous abortions. Patients and controls were recruited during pregnancy before fetal outcome was known. For each pregnancy, data on maternal epilepsy and antiepileptic drug use, family history, obstetric history and intoxications were collected during pregnancy. Stillbirths and neonatal deaths were included. At birth, one and four years, physical examination was performed by a paediatrician according to a standardized protocol. The endpoints for examination were major and minor abnormalities including body measurements, occurrence of neural tube defects, cleft lip and palate,

Table 4.1 *Description of the individual studies.*

	Germany, Berlin	Germany, Magdeburg	Finland, Helsinki	Netherlands, Rotterdam	Netherlands, Epilepsy Institutes
Year	1979 - 1990	1979 - 1987	1976 - 1979	1985 - 1990	1972 - 1990
Number AED exposed pregnancies	150	42	106	305	618
Number non-epileptic pregnancies	116	42	-	-	-
Matching criteria	maternal age parity social class smoking abortions	maternal age parity social class smoking abortions sex obst. clinic	-	-	-
Time of matching	during pregnancy	after delivery	-	-	-
Exclusion criteria	immature delivery	stillbirth and neonatal deaths non-epileptic controls with family history of epilepsy	immature delivery	-	-
Endpoints	major and minor congenital abnormalities and body measurements	major and minor congenital abnormalities and body measurements	major and minor congenital abnormalities and body measurements	major congenital abnormalities and body measurements	major congenital abnormalities and body measurements
Time of examination	birth, 1 and 4 years of age	birth, 1.5 and 5 years of age	birth, 1.5 and 5.5 years of age	0-3 months	0-3 months
Examined by	paediatrician	paediatrician	paediatric neurologist	gynaecologist or paediatrician	gynaecologist or paediatrician
Diagnosis of epilepsy by	neurologist	neurologist	neurologist	neurologist	neurologist
Number of mothers AED-exposed	123	32	97	261	411
Number of mothers without epilepsy	116	42	-	-	-
Exposure information	prospective	prospective	prospective	prospective	prospective

skeletal abnormalities, abdominal defects, genito-urinary defects, cardiac defects and dysmorphic features.

Helsinki, Finland

The study was conducted between 1976 and 1979[25] and comprised 97 mothers with epilepsy. Included were 106 antiepileptic drug exposed pregnancies (table 4.1). Only patients whose epilepsy diagnosis was confirmed by a neurologist and in whom the first seizure occurred before pregnancy, were included. Time of recruitment was during 7-24 weeks of pregnancy; all maternity units were asked to refer patients with epilepsy for the study to the Helsinki University City hospital. Patients with an immature delivery (pregnancy duration between 16-24 weeks) were excluded, but stillbirth and neonatal death were not exclusion criteria. Data on control pregnancies were not available for this reanalysis. For each pregnancy, data on maternal epilepsy and antiepileptic drug use, family history, obstetric history and smoking habits were collected. At birth, 1,5 and 5.5 years of age the child was examined by a paediatric neurologist according to a standardized protocol.[26] The endpoints for examination were major and minor abnormalities including body measurements, occurrence of neural tube defects, cleft lip and palate, skeletal abnormalities, abdominal defects, genito-urinary defects, cardiac defects and dysmorphic features.

Magdeburg, Germany

The study was conducted between 1979 and 1987 according to a protocol similar to that of the study preformed in Berlin.[27,28] There were 32 mothers with epilepsy with 42 antiepileptic drug exposed pregnancies (table 4.1). The diagnosis of epilepsy was always confirmed by a neurologist. In all patients but four the first seizure occurred before pregnancy. Patients were referred to the coordinating neuropaediatrician by two obstetric departments. The first delivery after birth of the exposed infant was selected as a control pregnancy (n=42). The matching criteria were sex, obstetric clinic, maternal age at delivery, parity, social class, smoking habits and previous abortions. Controls with a positive family history of epilepsy were excluded. Recruitment was carried out during pregnancy. Patients and controls with stillbirths or neonatal deaths were excluded, since the primary endpoint of the study was postnatal development. Data of maternal epilepsy and antiepileptic drug use, family history, obstetric history and intoxications were collected. At birth, one and a half and five years physical examination was performed by a paediatrician according to a standardized protocol. The endpoints for examination were major and minor abnormal-

ities including body measurements, occurrence of neural tube defects, cleft lip and palate, skeletal abnormalities, abdominal defects, genito-urinary defects, cardiac defects and dysmorphic features.

Rotterdam, The Netherlands

The study was conducted in the period 1985-1990 and comprised 261 women with epilepsy.[23,29-31] These women were consecutively referred to the outpatient clinic for prenatal diagnosis of the University Hospital Rotterdam, because of epilepsy with antiepileptic drug (or without antiepileptic drug) use. Recruitment was carried out before the fourth month of pregnancy. Only patients whose epilepsy diagnosis was confirmed by a neurologist were included. Data were available for 305 antiepileptic drug exposed (table 4.1). Amniocentesis or structural ultrasound, and in most patients both, were performed. Some pregnancies were interrupted because of major congenital abnormalities discovered during prenatal diagnosis. These pregnancies were also included in the study. No control pregnancies were selected. Data on maternal epilepsy and antiepileptic drug use, family history, obstetric history and intoxications were collected. Pregnancies ending in stillbirth or neonatal death were included. Neonatal examination was performed by a gynaecologist or paediatrician and defects observed within the first three months of life were included. The main endpoints were major congenital abnormalities including body measurements, occurrence of neural tube defects, cleft lip and/or palate, skeletal abnormalities, abdominal defects, genito-urinary defects, cardiac defects and dysmorphic features.

Institutes of Epilepsy, The Netherlands

This cohort comprised 411 women with epilepsy, derived from one of 14 outpatient clinics of the Special Centres for Epilepsy in The Netherlands (Instituut voor Epilepsie bestrijding "Meer en Bosch" - "De Cruquiushoeve", Heemstede; Epilepsiecentrum Kempenhaeghe, Heeze; Dr. Hans Bergerkliniek, Breda), in the period 1972-1990. In these centres, approximately 7% of all patient with epilepsy in the Netherlands are treated. Included were a total of 618 consecutive antiepileptic drug treated pregnancies (table 4.1). The cohort can be subdivided into three cohorts (A, B, C). The first study (cohort A) was conducted between 1972 and 1979 and comprises 151 antiepileptic drug exposed pregnancies.[32-34] The second study (cohort B) was conducted between 1980-1985 and comprises 172 antiepileptic drug exposed pregnancies.[11] The remaining pregnancies (cohort C) were collected between 1985 and 1990 and consist of 295 antiepileptic drug exposed pregnancies (not published before). Diagnosis

of epilepsy was confirmed by a neurologist. No control pregnancies were selected. Recruitment was carried out during or before pregnancy, and antiepileptic drug exposure was monitored during pregnancy. All abortions, premature deliveries and stillbirths are included. Data on maternal epilepsy and antiepileptic drug use, family history, obstetric history and intoxications were collected by the attending neurologist and forms were completed at the first visit to the outpatient clinic after delivery (usually three - five months after delivery). The neonatal examination was performed by a gynaecologist or paediatrician and major congenital abnormalities discovered within three months after birth were used in the analysis. The main endpoints were major congenital abnormalities including body measurements, occurrence of neural tube defects, cleft lip and/or palate, skeletal abnormalities, abdominal defects, genito-urinary defects, cardiac defects and dysmorphic features.

Assessment of abnormalities

In the present analysis, we defined major congenital abnormalities as an abnormality of an essential embryonal structure, present at birth or discovered during the first three months of age and/or requiring significant therapy before the first year of life. Some examples of major congenital abnormalities under this definitions are: neural tube defects (e.g. spina bifida aperta with/without hydrocephalus), congenital heart defects (e.g. ventricular septal defect), hypospadias, cleft lip and/or palate, pre- and/or post-axial polydactyly, club foot or a congenital hip dysplasia requiring plaster therapy, and inguinal hernia (only when requiring an operation).

Data analysis

The raw data of the studies were pooled and reanalysed. The data were analyzed in two ways. Firstly, the occurrence of major congenital abnormalities associated with maternal epilepsy and antiepileptic drug exposure were compared to control pregnancies. As the latter were only available for the Berlin and Magdeburg studies, this analysis was limited to these two studies. Multiple logistic regression was performed to estimate the relative risk (RR) using all non-epileptic controls as a reference and adjusting for the matching variables by including them in the regression model. Relatives risks are presented with a 95% confidence interval (CI), which will exclude the value 1 in case of statistical significance ($p<0.05$).

Secondly, risks associated with specific antiepileptic drug regimens were compared between pregnancies exposed to different regimens. Relative risks were used to quantify the strength of the association and presented with 95% confidence intervals.

Multiple logistic regression analysis was used to adjust for putative confounding variables such as maternal age, parity, social class, sex of the child, study site, type of epilepsy and dose of medication. If antiepileptic drugs were used in sufficient numbers, we tested for the presence of a dose-response relationship, with cut-off points based on tertiles. For this analysis no data were available from the Helsinki study.

Results

The five studies differed with regard to age at birth, parity, social class or sex of the child (table 4.2). Pregnancies were found to be at younger age in Germany and older age in Rotterdam. There were more nulliparae in the Dutch Epilepsy Institutes and Germany. There were fewer skilled manual labourers in the Rotterdam study.

The distribution of the different drug regimens for each centre, with the percentages of major congenital abnormalities for each regimen, is shown in table 4.3. There were differences in prescription regimens between the centres. In the Rotterdam study and the Dutch institutes of epilepsy there was a tendency towards more frequent prescription of carbamazepine, valproate, and combination therapies, whereas phenytoin and phenobarbital were prescribed less frequently compared to other centres. In Berlin and Magdeburg, phenytoin and primidone were prescribed more often than carbamazepine and valproate. In Helsinki the most frequently prescribed drugs were phenytoin and carbamazepine. Also, the risk of major congenital abnormalities differed significantly between centres. Significantly more major congenital abnormalities were found in Berlin (16%) and Magdeburg (14%) than in the other centres (table 4.3).

Firstly, we compared the risks of major congenital abnormalities in antiepileptic drug-exposed pregnancies to matched control pregnancies using the data from the studies from Berlin and Magdeburg (table 4.4). Overall we found a significantly increased risk of major congenital abnormalities in children of mothers with epilepsy using antiepileptic drugs during pregnancy, compared to children of healthy controls (RR 2.3, CI : 1.2 - 4.7; not in table). Moreover the risk of major congenital abnormalities was significantly increased in children of women using carbamazepine (RR 4.9, CI: 1.3-18.0) and in children exposed to valproate (RR 4.9, CI: 1.6-15.0) during pregnancy. Most other therapies also showed an increased relative risk, although not significant. However, the number of women using these antiepileptic drugs was very small, in particular for phenobarbital, and most regimens of polytherapy. When adjusting for maternal age, sex of the child, social class or parity of the mother, or type of maternal epilepsy in our multiple logistic regression analysis, none of the relative risks shown in table 4.4 changed materially (not shown in table).

Table 4.2 *Description of the study population.*

Characteristics	Germany, Berlin and Magdeburg*		Finland, Helsinki	Netherlands, Rotterdam	Epilepsy Institutes
	AED-exposed	Non-epileptic controls			
Number of pregnancies	192	158	106	305	618
Age:					
<20	18 (9%)	11 (7%)	4 (4%)	8 (2%)	5 (1%)
20-24	72 (38%)	64 (41%)	28 (26%)	60 (20%)	137 (22%)
25-29	68 (35%)	51 (32%)	45 (42%)	103 (34%)	297 (48%)
30-34	28 (15%)	25 (16%)	20 (19%)	97 (32%)	146 24%)
35+	6 (3%)	7 (4%)	9 (9%)	37 (12%)	33 (5%)
Parity:					
0	82 (42%)	72 (46%)	-	121 (40%)	311 (50%)
1	57 (30%)	59 (37%)	-	108 (35%)	210 (34%)
2+	52 (27%)	26 (16%)	-	74 (24%)	97 (16%)
unknown	1 (1%)	1 (1%)	-	2 (1%)	-
Social class:					
academic degree	3 (2%)	3 (2%)	15 (14%)	17 (6%)	-
white collar	41 (21%)	29 (19%)	33 (31%)	102 (33%)	-
skilled manual	104 (54%)	106 (67%)	45 (43%)	88 (29%)	-
unskilled manual	39 (20%)	18 (11%)	13 (12%)	37 (12%)	-
unknown	5 (3%)	2 (1%)		61 (20%)	-
Sex:					
Male	103 (54%)	84 (53%)	52 (49%)	148 (48%)	299 (48%)
Female	89 (46%)	74 (47%)	54 (51%)	156 (51%)	279 (45%)
Unknown†	-	-	-	1 (0.3%)	40 (7%)

* 150 antiepileptic drug (AED) exposed and 116 non-epileptic control pregnancies were derived from Berlin; 42 AED exposed and 42 non-epileptic control pregnancies were derived from Magdeburg
† miscarriage, no sex determination

Table 4.3 *Drug regimens and occurrence of major congenital anomalies in antiepileptic drug-exposed pregnancies in different study centres.(*)*

Exposures	Germany,		Finland,	Netherlands,		Total
	Berlin	Magdeburg	Helsinki	Rotterdam	Epilepsy Institutes	
carbamazepine (cbz)	3/10 (30%)	1/4 (25%)	2/18 (11%)	5/115 (4%)	11/133 (8%)	22/280 (8%)
ethosuximide (esm)	1/2 (50%)	-	-	0/2 (0%)	0/9 (0%)	1/13 (8%)
phenobarbital (pb)	0/5 (0%)	1/1 (100%)	-	3/18 (17%)	1/24 (4%)	5/48 (10%)
phenytoin (pht)	4/28 (14%)	1/5 (20%)	4/46 (9%)	0/29 (0%)	0/33 (0%)	9/141 (6%)
primidone (prm)	2/27 (10%)	1/12 (8%)	0/1 (0%)	-	1/3 (33%)	4/43 (9%)
valproate (vpa)	4/16 (25%)	2/5 (40%)	-	7/64 (11%)	3/99 (3%)	16/184 (9%)
cbz+clonazepam (clp)	0/2 (0%)	-	-	2/7 (29%)	0/2 (0%)	2/11 (18%)
cbz+vpa	-	-	1/1 (100%)	2/13 (15%)	6/65 (9%)	9/79 (11%)
pht+cbz	1/2 (50%)	-	1/9 (11%)	0/6 (0%)	2/27 (7%)	4/44 (9%)
pht+pb	2/15 (13%)	-	2/10 (20%)	1/7 (14%)	0/8 (0%)	5/40 (13%)
pht+vpa	1/2 (50%)	0/1 (0%)	0/5 (0%)	0/2 (0%)	1/8 (13%)	2/18 (11%)
pb+cbz	-	-	0/1 (0%)	0/10 (0%)	1/16 (6%)	1/27 (4%)
pb+esm	1/3 (33%)	-	-	-	1/2 (50%)	2/5 (40%)
pb+vpa	1/2 (50%)	-	-	0/5 (0%)	2/9 (22%)	3/16 (19%)
prm+vpa	1/8 (13%)	0/5 (0%)	-	-	-	1/13 (8%)
vpa+clp	-	-	-	0/3 (0%)	1/3 (33%)	1/6 (17%)
vpa+esm	1/2 (50%)	-	-	0/3 (0%)	2/34 (6%)	3/39 (8%)
cbz+vpa+clp	-	-	-	0/1 (0%)	1/4 (25%)	1/5 (20%)
pht+pb+cbz+vpa	-	-	-	-	3/7 (43%)	3/7 (43%)
others	3/26 (12%)	0/9 (0%)	0/15 (0%)	2/20 (10%)	8/132 (6%)	13/202 (6%)
Total	25/150 (17%)	6/42 (14%)	10/106 (9%)	22/305 (7%)	46/618 (7%)	108/1221 (9%)

* Numbers are abnormalities/total exposed

Table 4.4 *Relative risk of major congenital anomalies: comparison AED-exposed and non-epileptic controls* *.

Exposures	pregnancies(†)	RR	95% CI
non-epileptic controls	12/158 (8%)	1.0	reference
carbamazepine	4/14 (29%)	4.9	1.3 - 18.0
phenobarbital	1/6 (17%)	2.4	0.3 - 23.0
phenytoin	5/33 (15%)	2.2	0.7 - 6.7
primidone	3/39 (8%)	1.0	0.3 - 3.8
valproate	6/21 (29%)	4.9	1.6 - 15.0
phenytoin+phenobarbital	2/15 (13%)	1.8	0.4 - 9.4
primidone+valproate	1/13 (8%)	1.0	0.1 - 8.6
others	8/51 (16%)	2.1	0.8 - 5.4

* Data only available in studies of Berlin and Magdeburg.
† Numbers are abnormalities/total exposed

Secondly, we compared the risks of major congenital abnormalities between the different drug regimens using the data of all centres. We first calculated the risk of major congenital abnormalities in the different drug regimens, using all antiepileptic drug treated pregnancies pooled from all five centres (table 4.5). The drug (monotherapy) with the lowest percentage of major congenital abnormalities (i.e. phenytoin) was used as a reference for comparisons with other drug regimens. In the crude overall analysis there were no significant differences in relative risk of major congenital abnormalities between the different monotherapy drug regimens. When studying neural tube defects in valproate monotherapy users though, the absolute risk of neural tube defects was 3.8% compared to 1.0% in carbamazepine users and 0% in other monotherapy regimens. For the polytherapies studied only the combinations of phenobarbital and ethosuximide (RR 9.8, CI: 1.4-67.3; n=5) and phenytoin, phenobarbital, carbamazepine and valproate (RR 11.0, CI: 2.1-57.6; n=7) showed a significantly increased risk of major congenital abnormalities compared to phenytoin monotherapy, but these drug combinations were used by only a very small number of women. When adjusting for confounders such as type of epilepsy (table 4.5), study centre and social economic status, only study centre influenced the effects of the drug regimens (not in table). The risks of major congenital abnormalities for the offspring of women using valproate (RR 3.7, CI: 1.2-11.8), carbamazepine (RR 2.8, CI: 1.1-7.3) and phenobarbital (RR 4.2, CI: 1.0-18.6) monotherapy were significantly increased, when adjusting for study centre. An increased risk of major congenital abnormalities for valproate users was found in all studies except the Helsinki study, in which

Table 4.5 *All centres: Relative risk of major congenital anomalies (comparison of different antiepileptic drug regimens with phenytoin).*

Exposures [1]	N (all centres)	RR (crude)	95% CI	RR (adjusted *)	95% CI	N (first pregnancies)	RR (first pregnancies)	95% CI
phenytoin (pht)	9/141 (6%)	1.0	reference	1.0	reference	8/118	1.0	reference
carbamazepine (cbz) [2]	22/280 (8%)	1.3	0.6 - 2.8	1.2	0.5 - 2.7	17/210	1.2	0.5 - 2.9
ethosuximide (esm)	1/13 (8%)	1.2	0.1 - 10.7	0.6	0.1 - 6.8	0/9	-	-
phenobarbital (pb)[3]	5/48 (10%)	1.7	0.5 - 5.4	1.9	0.5 - 6.9	5/37	2.2	0.7 - 7.1
primidone (prm)	4/43 (9%)	1.5	0.4 - 5.2	1.0	0.3 - 4.0	4/32	2.0	0.6 - 7.1
valproate (vpa)[4]	16/184 (9%)	1.4	0.6 - 3.3	1.5	0.6 - 4.0	10/121	1.2	0.5 - 3.3
cbz+clp	2/11 (18%)	3.3	0.6 - 17.6	3.6	0.6 - 19.7	1/5	3.4	0.3 - 35.3
vpa+cbz	9/79 (11%)	1.9	0.7 - 5.0	1.9	0.7 - 5.0	5/48	1.6	0.5 - 5.2
pht+cbz	4/44 (9%)	1.5	0.4 - 5.1	1.5	0.4 - 5.2	4/34	1.8	0.5 - 6.6
pht+pb	5/40 (13%)	2.1	0.7 - 6.7	2.0	0.6 - 6.5	5/34	2.4	0.7 - 7.9
pht+vpa	2/18 (11%)	1.8	0.4 - 9.4	1.6	0.3 - 8.4	1/14	1.1	0.1 - 9.3
pb+cbz	1/27 (4%)	0.6	0.1 - 4.7	0.5	0.1 - 3.9	1/19	0.8	0.1 - 6.6
pb+esm	2/5 (40%)	9.8	1.4 - 67.3	7.5	1.0 - 56.0	1/3	6.9	0.6 - 86.4
pb+vpa	3/16 (19%)	3.4	0.8 - 14.2	2.4	0.5 - 12.2	3/13	4.1	0.9 - 18.3
prm+vpa	1/13 (8%)	1.2	0.1 - 10.7	0.8	0.1 - 7.4	1/9	1.7	0.2 - 15.8
vpa+clonazepam (clp)	1/6 (17%)	2.9	0.3 - 28.4	2.5	0.2 - 25.2	1/6	2.8	0.3 - 27.1
vpa+esm	3/39 (8%)	1.2	0.3 - 4.8	0.6	0.1 - 3.2	3/27	1.7	0.4 - 7.0
cbz+vpa+clp	1/5 (20%)	3.7	0.4 - 37.0	3.7	0.4 - 37.6	1/2	13.8	0.8 - 248.0
pht+pb+cbz+vpa	3/7 (43%)	11.0	2.1 - 57.6	13.8	2.5 - 76.9	2/6	6.9	1.1 - 44.2
others †	13/202 (6%)	1.0	0.4 - 2.4	0.9	0.4 - 2.3	13/149	1.3	0.5 - 2.2

† all regimens consisting of 4 pregnancies or less
* adjusted for type of epilepsy
1) RR calculation after adjustment for centre were limited by too small numbers, except for carbamazepine, phenobarbital, and valproate.
2) RR for carbamazepine adjusted for centre: 2.8 (1.1 - 7.3)
3) RR for phenobarbital adjusted for centre: 4.2 (1.0 - 18.6)
4) RR for valproate adjusted for centre: 3.7 (1.2 - 11.8)

valproate was not prescribed in monotherapy. For the other drug regimens, there was no evidence for confounding by study centre. We did not find a significant evidence for an association between any type of epilepsy and the risk of major congenital abnormalities in the offspring. In order to examine the influence of multiple pregnancies of women with epilepsy in the study, we performed an analysis in which only the first pregnancy of a women ascertained in the study was included (table 4.5). This did not change the results.

Finally, we evaluated the possibility of a dose-dependent association (figure 4.1). Due to the small categories, these analyses are not adjusted for study centre, maternal

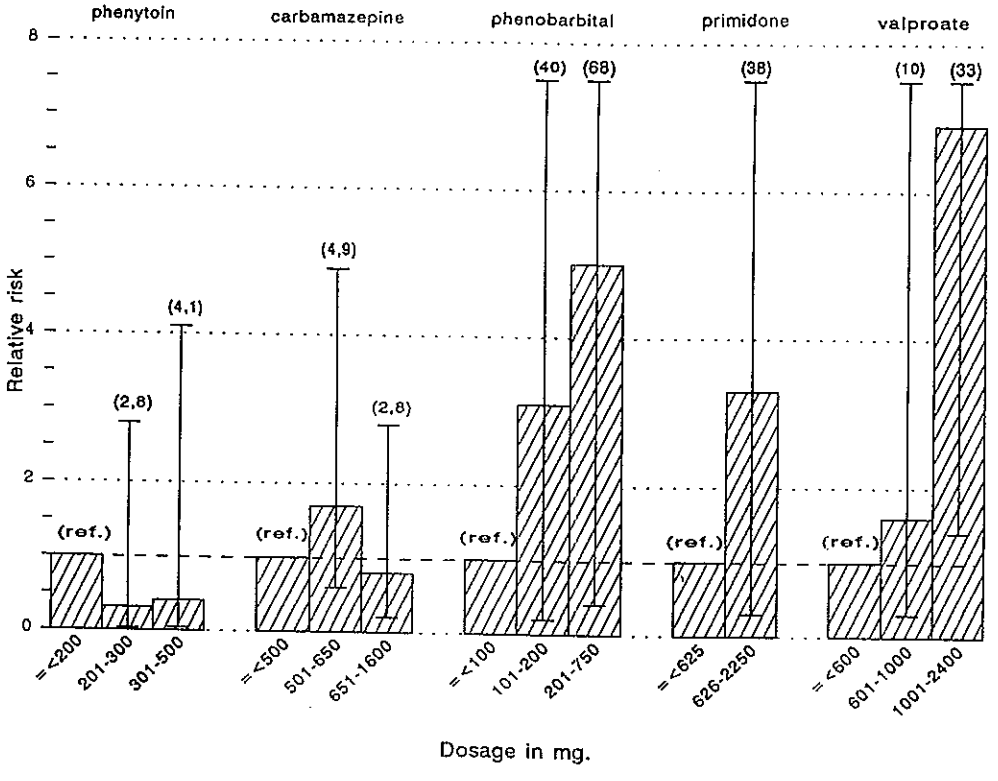

Figure 4.1 *Risk of major congenital abnormalities by increasing dose of the drug regimen in monotherapy (cut-off point at 33.3% and 66.6%). Above the bars, the upper limit for the 95% confidence interval is given. Included are all drug regimens used in 30 pregnancies or more.*

age, sex of the child, social class, parity of the mother or maternal epilepsy. Among valproate users, a significant increase in risk of major congenital abnormalities was found for offspring of women using more than 1000 mg a day as compared to those using less than 600 mg a day (RR 6.8, CI 1.4-32.7). The major congenital abnormalities found in the offspring of women using 1000 mg or more were spina bifida with/without hydrocephalus (n=5; 28%), ventricular septum defect (n=1; 6%), Fallot tetralogy (n=1; 6%), atrial septum defect (n=1; 6%), craniosynostosis (n=1; 6%), a combination of meningomyelocele, microcephaly and inguinal hernia (n=1; 6%) and a combination of aplasia of the first rib and hypersegmentation of the manubrium sterni (n=1; 6%). For phenobarbital monotherapy there also seemed to be an increase in risk with increasing dose, but these differences were not significant. Abnormalities occurring twice or more are summarized in tables 4.6.a and 4.6.b.

Table 4.6.a *Major congenital abnormalities occurring twice or more with use of monotherapy (denominator ≥ 20)*

Major congenital abnormalities	cbz	vpa	pht	pb	prm	others	any (≥2)
Total exposures	280	184	141	48	43	17	713
Inguinal hernia	4	2*	1	-	3	1	11
Spina bifida aperta ± hydrocephalus	3¢	7*	-	-	-	-	-
Congenital heart defect	-	2	3†	3‡	-	-	8
Cleft lip +/- palate	3§	-	1†	2	1	-	7
Pre-/post-axial polydactyly	3¶	2#	2	-	-	-	6
Hypospadias	3§ $	1	1	-	-	-	5
Club foot	2	1	-	-	-	-	3
Preauricular ear skin tag	1£	-	1	-	-	1**	3
Hipluxation	2	-	-	-	-	-	2
Microcephaly	-	1*	1	-	-	-	2
Ptosis	2£ $	-	-	-	-	-	2
Others	2o	2¥	1♮	-	-	1*f*	6

* one case with meningomyelocele, inguinal hernia and microcephaly
† one case with congenital heart defect and cleft lip + palate
‡ one case with congenital heart defect, radius aplasia and hemivertebrae 1, 3 ,5
§ one case with cleft lip, hypospadias and hydrocephalus
¶ one case with oesophageal atresia and pre-axial polydactyly
\# one case with triphalangeal thumb and hemimelia
$ one case with hypospadias and ptosis
£ one case with preauricular ear skintag and ptosis
** one case with preauricular fistel
o one of each: hypertrophic pylorus stenosis
asymmetric crying face
¥ one of each: craniosynostosis
aplasia first rib and hypersegmentation manubrium sterni
♮ one case with congenital megacolon
f one case with chylothorax and persistent fetal circulation
¢ palpable defect in sacral spinal arches at birth confirmed with X-ray, with normal overlying skin.

Table 4.6.b *Major congenital abnormalities occurring twice or more with use of polytherapy (denominator ≥ 20)*

Major congenital abnormalities	cbz	vpa	pht	pb	prm	others	any (≥2)
Total exposures	280	184	141	48	43	17	713
Inguinal hernia	4	2*	1	-	3	1	11
Spina bifida aperta ± hydrocephalus	3¢	7*	-	-	-	-	-
Congenital heart defect	-	2	3†	3‡	-	-	8
Cleft lip +/- palate	3§	-	1†	2	1	-	7
Pre-/post-axial polydactyly	3¶	2#	2	-	-	-	6
Hypospadias	3§ $	1	1	-	-	-	5
Club foot	2	1	-	-	-	-	3
Preauricular ear skin tag	1£	-	1	-	-	1**	3
Hipluxation	2	-	-	-	-	-	2
Microcephaly	-	1*	1	-	-	-	2
Ptosis	2£ $	-	-	-	-	-	2
Others	2o	2¥	1♮	-	-	1ƒ	6

* one case with meningomyelocele, inguinal hernia and microcephaly
† one case with congenital heart defect and cleft lip + palate
‡ one case with congenital heart defect, radius aplasia and hemivertebrae 1, 3 ,5
§ one case with cleft lip, hypospadias and hydrocephalus
¶ one case with oesophageal atresia and pre-axial polydactyly
\# one case with triphalangeal thumb and hemimelia
$ one case with hypospadias and ptosis
£ one case with preauricular ear skintag and ptosis
** one case with preauricular fistel
o one of each: hypertrophic pylorus stenosis
asymmetric crying face
¥ one of each: craniosynostosis
aplasia first rib and hypersegmentation manubrium sterni
♮ one case with congenital megacolon
ƒ one case with chylothorax and persistent fetal circulation
¢ palpable defect in sacral spinal arches at birth confirmed with X-ray, with normal overlying skin.

Discussion

The findings in our study show an overall increased risk of major congenital abnormalities in children of mothers with epilepsy using antiepileptic drugs during pregnancy, compared to children of healthy controls. The most pronounced increase in risk was found for children exposed intra-uterinely to valproate or carbamazepine in monotherapy. When comparing different antiepileptic drug regimens during pregnancy, risks of major congenital abnormalities were significantly increased for the rare combination of phenobarbital and ethosuximide and the combination of phenytoin, phenobarbital, carbamazepine and valproate. In an analysis adjusted for study centre, this risk was also significantly increased for carbamazepine, phenobarbital and valproate in monotherapy. The risk associated with valproate monotherapy appeared to be dose dependent, with the offspring of mothers using more than 1000 mg/day

being at an increased risk, in particular of neural tube defects. The risk associated with phenobarbital also appeared to be dose dependent.

As our findings are based on non-randomized studies, biases may have occurred. In none of the studies pooled, paediatricians or other investigators assessing the presence of major congenital abnormalities were blind to the exposure status. Further, in this reanalysis data of studies were pooled which differed considerably in methodology including diagnosis and ascertainment of patient. For this reanalysis, the raw data were obtained from the centres and we standardized the criteria for major congenital abnormalities. However, the fact that stillbirths and neonatal deaths were not included in the study from Magdeburg could not be adjusted for. It is important to note that this study is relatively small (n=42) and the effect of the exclusion of stillbirths and neonatal deaths on the risk estimates is therefore probably limited. Furthermore, the Magdeburg group had no pregnancies that had to be excluded because of stillbirth or neonatal death during the study period.

Centres differed with respect to medication prescription and risks of major congenital abnormalities. Differences in risk of abnormalities may be explained in part by differences in diagnostic procedures between centres. As this may confound the analysis, we adjusted for study centre in the pooled analysis and studied the association between antiepileptic drugs and major congenital abnormalities (according to the standardised criteria) also within each study centre. A higher risk of major congenital abnormalities for those exposed to valproate was found consistently in all centres that studied this drug, although this was not significant in the individual centres, probably due to the small number of exposed. This suggests that if the association is due to bias, this must have occurred similarly in all studies, which is plausible only in the case of confounding by indication. Here confounding by indication implies that certain types of epilepsy, that increase the risk of abnormalities by themselves, may require certain antiepileptic drugs leading to a spurious association between the antiepileptic drugs and the risk of major congenital abnormalities. Indeed, there was evidence for a relation between the type of epilepsy and the prescription of drugs in this study. Patients with generalized epilepsy were prescribed more often the monotherapies valproate, ethosuximide, phenobarbital or primidone and the combinations of valproate and phenobarbital, primidone and carbamazepine or valproate and ethosuximide. Patients with partial epilepsy more often used carbamazepine monotherapy or the combinations of carbamazepine and phenytoin, carbamazepine and valproate or carbamazepine and clonazepam. Although it is difficult to exclude confounding by indication in an observational study, we found no significant evidence for an association between any

type of epilepsy and major congenital abnormalities, suggesting that type of epilepsy is not likely to explain the results. Finally, bias may be related to the fact that multiple pregnancies of a woman were included. We therefore performed an analysis in which only the first pregnancy of a woman ascertained in the study was included. This did not change any of our conclusions.

An increased risk of major congenital abnormalities has previously been reported for valproate. About ten years after the introduction of valproate, the possibility of teratogenic effects became evident, and an association with neural tube defect was observed in mice.[35,36] Subsequently reports of children with neural tube defects after prenatal exposure to valproate were published.[33,37-41] A risk of 1 to 2% was estimated on the basis of retrospective studies[33,38,42] and a review of several small prospective cohort studies.[41] The prospective study by Omtzigt et al.[23] suggested a risk as high as 6%. In the pooled analysis, the risk of neural tube defects in offspring of women using valproate was 3.8%. This study, as well as animal experiments[43], suggest that the dose is important in the increased risk of neural tube defects. An association between hypospadias and valproate has also been suggested.[11,33,44] The current study is inconclusive with regard to this finding (n=1). A risk of neural tube defects for children exposed to carbamazepine was 1.0%, which is very similar to the 0.5-1% risk reported earlier.[10]

This reanalysis of data from five prospective studies shows that valproate is consistently associated with an increased risk of major congenital abnormalities in the offspring. An important advantage of the present study is that we were able to reanalyse data of prospective European studies using uniform criteria for the diagnosis of major congenital abnormalities and address a dose-response relationship between the occurrence of these abnormalities and the use of antiepileptic drugs. For carbamazepine, no evidence for a dose-response relationship was found, while risk remained non-significant for phenobarbital. Our study shows that, in particular, the offspring of women using more than 1000 mg/day of valproate during pregnancy appear to be at increased risk. Based on the risk estimates one may recommend to avoid valproate monotherapy during pregnancy if other antiepileptic drugs can achieve satisfactory seizure control, or when unable to change to other antiepileptic drugs, to use daily dosages below 1000 mg/day, whenever possible in view of effective seizure control. Although we have pooled the data of five studies, the number of women exposed to a certain drug regimen, especially drug combinations, remains small for a substantial number of antiepileptic drugs, leading to instable risk estimates. In spite of the standardized case-definition and gain of statistical power obtained in this reanalysis,

the interpretation of our findings is still limited because of the differences in prescription and case-ascertainment between centres. Therefore, standardized single or multi-centre studies with larger numbers of antiepileptic drug exposed pregnancies remain necessary to further quantify the effect of the other antiepileptic drugs in the etiology of major congenital abnormalities in the offspring of women with epilepsy.

Finally, we would encourage multi-centre prospective and population-based studies of pregnancy outcome to be carried out, according to a standardized study protocol and standardized study procedures, such as ascertainment procedures, assessment of etiological factors and outcome (including definition of outcome), in- and exclusion criteria, and selection of controls (if appropriate). This is especially relevant for the coming decades, in view of the high number of new antiepileptic drugs that are currently entering the market, and for which no human clinical safety data with respect to use during pregnancy are available.

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Chapter 5

A retrospective population-based follow-up study in the Netherlands

Chapter 5.1

Maternal epilepsy and major congenital abnormalities in the offspring

5.1 Maternal epilepsy and major congenital abnormalities in the offspring

Summary

Antiepileptic drugs have been associated with a two- to three-fold increased risk of major congenital abnormalities in the offspring. This risk has mainly been attributed to antiepileptic drugs, but questions remain whether the maternal epilepsy, or the occurrence of seizures during pregnancy also play a role. To assess the risk of major congenital abnormalities in the offspring of women with epilepsy a retrospective cohort study was performed, comprising offspring of women with epilepsy born between 1972-1994 in 28 hospitals in four provinces in the Netherlands.

Offspring exposed to antiepileptic drugs in first trimester of pregnancy had an increased risk of major congenital abnormalities (relative risk (RR) 2.6, 95% confidence interval (CI): 1.6-4.1). Children prenatally exposed to antiepileptic drugs, but **not** during first trimester of pregnancy, also showed an increased risk of major congenital abnormalities. In this group major congenital abnormalities were found to be associated with maternal partial epilepsy (RR 5.1, CI: 1.5-17.4) and seizures during first trimester (RR 7.2, CI: 1.6-32.2). Children of mothers with epilepsy not exposed to antiepileptic drugs throughout pregnancy showed no increased risk of major congenital abnormalities compared to the non-epileptic control population.

Our study of 4107 pregnancies shows a teratogenic effect of antiepileptic drug treatment during pregnancy. Furthermore, it strongly suggests that a subpopulation of women with only second and/or third trimester exposure to antiepileptic drugs are at a relatively high risk of having malformed offspring, in particular associated with partial epilepsy or the occurrence of seizures during pregnancy.

Introduction

Since the teratogenic effects of antiepileptic drugs first became suspected,[1,2] several case-control studies,[3-6] and retrospective[7-11] and prospective[12-19] follow-up studies have been performed to assess the risk of major congenital abnormalities in the offspring of women with epilepsy. Most of these studies showed a two- to three fold increased risk of major congenital abnormalities in the offspring associated with antiepileptic drug use during pregnancy. Controversy exists whether this risk is attributable to the teratogenicity of the antiepileptic drug itself, to a genetic predisposition associated with epilepsy,[20,21] to seizures during pregnancy,[16,22] or a combination of these.[23,24] Although several studies have addressed these issues, conclusions were limited, often due to lack of sufficient numbers of treated and untreated pregnancies with epilepsy.[25-28]

We have performed a retrospective cohort study in 4107 pregnancies, aiming to assess the risks of major congenital abnormalities in the offspring of women with epilepsy both with and without exposure to antiepileptic drugs during pregnancy compared to matched non-epileptic controls.

Methods

The study comprised offspring of women with epilepsy, with or without antiepileptic drug use during pregnancy, born between 1972-1994 in 28 hospital in four provinces of the Netherlands. Using hospital delivery books, hospital delivery registration systems, national delivery registration systems (National Perinatal Data Base LVR), outpatient clinics for prenatal diagnosis, and obstetrical history, we aimed at ascertaining all deliveries with maternal epilepsy independent of outcome, including pregnancies terminated after prenatal diagnosis. Dysmature and premature deliveries were included, as well as stillbirths and pregnancies terminated because of severe fetal anomalies diagnosed prenatally. Included in the study are 1348 mothers with epilepsy and 2107 children born to these women, as well as 1955 matched non-exposed controls and 2000 children born to these women. Control pregnancies were matched to the exposed pregnancies for maternal age (+/- 2 years) and parity, and sex, year of birth and hospital of delivery of the child. The study protocol was approved by the Medical Ethical Committee of Erasmus University.

Data collected from medical records included general characteristics of the mother, information on pregnancy and child, obstetrical history, family history, epilepsy, medication and intoxications. Information on type of epilepsy was retrieved from obstetric or neurologic patient files or from correspondence with treating neurologists. Epilepsy of the mother was classified into generalized, partial or unknown.

Endpoints of the study were major congenital abnormalities in the offspring, defined as an abnormality of an essential embryonal structure, present at birth or discovered during the first six weeks of life. Examples of major congenital abnormalities according to this definition are: neural tube defects (e.g. spina bifida aperta with/without hydrocephalus), congenital heart defects (e.g. ventricular septal defect), hypospadias, cleft lip and/or palate, pre- and/or post-axial polydactyly, club foot or congenital hip dysplasia requiring plaster therapy or surgery, and inguinal hernia, but only when requiring surgery. Information on major congenital abnormalities was also retrieved from patient files and sometimes completed with information from the paediatrician.

The mothers with epilepsy were divided into five exposure groups. Group I *(first*

trimester exposure) includes women using antiepileptic drugs at least during the first trimester of pregnancy and possibly during the second and third trimester (921 women and 1411 children). Group II *(only second/third trimester exposure)* includes women who were only treated with antiepileptic drugs during the second and/or third trimester (79 women and 115 children). Group III *(unknown trimester)* includes women who were using antiepileptic drugs in pregnancy, without documentation in which trimester (54 women and 79 children). Group IV *(non-exposed epileptic)* includes women without antiepileptic drug use throughout pregnancy (244 women and 421 children). Group V *(unknown)* consists of 50 women (3.5%) with epilepsy (81 children) without any documentation about antiepileptic drug use during pregnancy. The latter group was not included in the analyses.

Data analysis

The occurrence of major congenital abnormalities in offspring with maternal epilepsy in the four exposure groups were compared to non-epileptic control pregnancies not treated with antiepileptic drugs. Relative risks (RR) were calculated, using all non-epileptic controls as a reference. Multiple logistic regression analysis was used to adjust for putative confounding variables such as maternal age, parity. Relative risks are presented with a 95% confidence interval (CI), which will exclude the value 1 in case of statistical significance ($p<0.05$).

Results

Baseline characteristics are presented in table 5.1.1. No significant differences were found between the five groups regarding age, parity, social class, sex of the child and miscarriages. There was a significant difference between group I *(first trimester exposure)* and group II *(only second/third trimester exposure)* regarding mean age at onset epilepsy (group II 18.2 versus group I 14.1, $p=0.0002$) and mean difference in years between onset of epilepsy and birth of child (group II 9.1 versus group I 13.6, $p<0.0001$). All women with second and/or third trimester antiepileptic drug use had onset of epilepsy before pregnancy and were on chronic antiepileptic drug medication, which was discontinued before pregnancy.

The frequencies and the relative risks of major congenital abnormalities in the epilepsy groups compared to the non-epileptic controls are shown in table 5.1.2. When adjusting relative risks for the matching variables maternal age and parity the results did not change. The risk of major congenital abnormalities was increased in all

Table 5.1.1 *Baseline characteristics of the study population.*

		Controls	Group I (first trimester exposure)	Group II (only second/third trimester exposure)	Group III (unknown trimester)	Group IV (non-exposed epileptic)
Number pregnancies		2000	1411	115	79	421
Age:	<20	69 (4%)	43 (3%)	3 (3%)	7 (9%)	24 (6%)
	20-24	484 (24%)	323 (23%)	34 (29%)	14(18%)	99 (24%)
	25-29	806 (40%)	593 (42%)	48 (42%)	34(43%)	160 (38%)
	30-34	483 (24%)	333 (24%)	23 (20%)	17(23%)	98 (23%)
	35+	158 (8%)	119 (8%)	7 (6%)	7(9%)	40 (9%)
Mean age at birth child (sd)		27.5 (4.7)	27.6 (4.7)	26.8 (4.8)	27.3 ((5.1)	27.4 (5.2)
Mean age at onset epilepsy (sd)		-	14.1 (7.3)	18.2 (8.9) *	15.3 (8.1)	13.4 (7.6)
Mean difference in years between birth child and onset of epilepsy (sd)		-	13.6 (7.8)	9.1 (9.0) **	11.9 (6.3)	14.0 (8.0)
Parity:	0	968 (48%)	648 (46%)	54 (47%)	38 (48%)	171 (41%)
	1	703 (35%)	498 (35%)	44 (38%)	27 (34%)	156 (37%)
	2+	329 (17%)	265 (19%)	17 (15%)	14 (18%)	94 (22%)
Sex:	female	953 (47%)	697 (48%)	53 (46%)	31 (39%)	203 (48%)
	male	1039 (52%)	727 (51.5%)	62 (54%)	48 (61%)	218 (52%)
	unknown	8 (1%)	5 (0.5%)	0 (0%)	0 (0%)	0 (0%)
Miscarriage:	0	1667 (84%)	1147 (81%)	99 (86%)	64 (81%)	341 (81%)
	1	265 (13%)	184 (13%)	13 (11%)	10 (13%)	68 (16%)
	2	47 (2%)	54 (4%)	3 (3%)	3 (4%)	6 (1.5%)
	3+	21 (1%)	26 (2%)	0 (0%)	2 (2%)	6 (1.5%)

* sd = standard deviation

Group II versus group I:

* $p = 0.0002$

** $p < 0.0001$

children exposed to antiepileptic drugs during pregnancy (group I, II and III). A significant effect was found only in group I *(first trimester exposure)*. No increase in risk was found for the offspring with maternal epilepsy not exposed to antiepileptic drugs (group IV).

Table 5.1.2 *Relative risk (95% confidence interval) of major congenital abnormalities in offspring of women with epilepsy (treated and not treated with antiepileptic drugs) compared to non-epileptic controls.*

Exposure	Crude		Adjusted for age and parity
	N* (%)	RR (95% CI)	RR (95% CI)
Non-epileptic controls	29/2000 (1.5%)	1 (reference)	1 (reference)
Group I (antiepileptic drugs in first trimester)	52/1411 (3.7%)	2.6 (1.6-4.1)	2.6 (1.6-4.1)
Group II (antiepileptic drugs only in second/third trimester)	4/115 (3.5%)	2.5 (0.9-7.1)	2.6 (0.9-7.7)
Group III (antiepileptic drugs in unknown trimester)	2/79 (2.5%)	1.8 (0.4-7.5)	1.6 (0.4-6.8)
Group IV (epilepsy without antiepileptic drugs)	7/421 (1.7%)	1.2 (0.5-2.6)	1.2 (0.5-2.8)

* numbers are abnormalities/total exposed pregnancies

In group I *(first trimester exposure)*, we found significantly increased risks of major congenital abnormalities for the offspring of mothers with generalized epilepsy (RR 3.3, CI: 1.8-5.9) and partial epilepsy (RR 2.4, CI: 1.3-4.4), as compared to non-epileptic controls (table 5.1.3). Furthermore, the risk of major congenital abnormalities was significantly increased for the offspring of women with seizures (RR 4.2, CI: 1.8-9.7) and without seizures (RR 2.4, CI: 1.5-4.0) during first trimester in group I *(first trimester exposure)*, the risk being highest for those with seizures.

In group II *(only second/third trimester exposure)*, we found a significantly increased risk of major congenital abnormalities in the offspring of mothers with partial epilepsy (RR 5.1, CI: 1.5 - 17.4), while it was not significantly increased for mothers with generalized epilepsy. The risk of major congenital abnormalities was significantly increased for offspring of women *with* seizures during first trimester (RR 7.2, CI: 1.6-32.2), while it was not significantly increased for mothers without seizures. In this group II *(only second/third trimester exposure)*, the frequency of seizures increased towards the end of pregnancy (18%, 24%, 41% in first, second and third trimester, respectively) due to an increase in number of different pregnancies in which

Table 5.1.3 *Relative risk (95% confidence interval) of major congenital abnormalities in the offspring of women with epilepsy stratified for type of epilepsy and seizures during first trimester of pregnancy, as compared to non-epileptic controls.*

	Group I Treated in first trimester		Group II Treated in second and/or third		Group III Treated, trimester unknown		Group IV Not treated	
	No (%)	RR (95% CI)	N (%)	RR (95% CI)	N (%)	RR (95% CI)	N (%)	RR (95% CI)
General	19/413 (4.6%)	3.3 (1.8-5.9)	1/35 (2.9%)	2.0 (0.3-15.1)	1/20 (5.0%)	3.6 (0.5-27.7)	3/88 (3.4%)	2.4 (0.7-8.0)
Partial	18/520 (3.5%)	2.4 (1.3-4.4)	3/43 (7.0%)	5.1 (1.5-17.4)	0/19 (0%)	-	2/124 (1.6%)	1.1 (0.3-4.7)
Unknown	15/478 (3.1%)	2.2 (1.2-4.1)	0/37 (0%)	-	1/40 (2.5%)	1.7 (0.2-13.1)	2/209 (1.0%)	0.7 (0.2-3.1)
Seizures 1st trimester -	34/996 (3.4%)	2.4 (1.5-4.0)	2/82 (2.4%)	1.7 (0.4-7.3)	2/56 (3.6%)	2.5 (0.6-10.8)	5/323 (1.5%)	1.1 (0.4-2.8)
Seizures 1st trimester +	7/114 (6.1%)	4.2 (1.8-9.7)	2/21 (9.5%)	7.2 (1.6-32.2)	0/7 (0%)	-	0/18 (0%)	-
Seizures 1st trimester unknown	11/291 (3.8%)	2.7 (1.3-5.4)	0/12 (0%)	-	0/16 (0%)	-	2/80 (2.5%)	1.7 (0.4-7.4)

* Numbers are abnormalities/total exposed pregnancies

seizures occurred only during the second or third trimester. This increase in seizure frequency was not associated with an increase of major congenital abnormalities. In 13 out of 73 women (18%) who experienced seizures somewhere during pregnancy, seizures continued to occur during pregnancy, despite restart of medication (table 5.1.4). Within group I *(first trimester exposure)* and group II *(only second/third trimester exposure)* exposure to maternal seizures during the first trimester of pregnancy showed a non-significantly increased relative risk of major congenital abnormalities compared to no maternal seizures of: 1.7 (CI: 0.7-3.9) and 4.2 (CI: 0.5-32.6) respectively.

Table 5.1.4 *Frequency of seizures during pregnancy stratified for trimester.*

	Seizures in pregnancy		
	First trimester No (%)	Second trimester No (%)	Third trimester No (%)
Group I (antiepileptic drugs in first trimester)	121/1411 (8.6%)	120/1411 (8.5%)	149/1411 (10.6%)
Group II (antiepileptic drugs only in second/third trimester)	21/115 (18.3%)	27/115 (23.5%)	47/115 (40.9%)
Group III (antiepileptic drugs in unknown trimester)	7/79 (8.9%)	6/79 (7.6%)	8/79 (10.1%)
Group IV (epilepsy without antiepileptic drugs)	18/421 (4.3%)	9/421 (2.1%)	22/421 (5.2%)

* numbers are pregnancies exposed to seizures/total pregnancies

To examine the influence of multiple pregnancies of women with epilepsy in the study, we performed an analysis in which only the first pregnancy of a woman entered in the study was used. The risk of major congenital abnormalities in the offspring in each exposure group did not change materially (not shown in table).

Discussion

Our study shows that first trimester exposure to antiepileptic drugs is significantly associated with major congenital abnormalities in the offspring. There was no difference in risk between the different types of epilepsy in this group. The risk of major congenital abnormalities was also increased for the offspring of women treated only in second and/or third trimester of pregnancy, but not during the first trimester. Within this group, partial epilepsy and the occurrence of one or more seizures during the first trimester of pregnancy were associated with a significantly increased risk of major congenital abnormalities. No increased risk was found among the offspring of

mothers with epilepsy without antiepileptic drug use during pregnancy as compared to non-epileptic controls.

Our study is based on medical records, and therefore data on a number of variables, such as time of treatment, type of epilepsy, and occurrence of seizures, were not available for some of the women. Since only obviously visible defects could be included, the frequency of congenital abnormalities in this study will probably be an underestimate of the actual frequency. However, this underestimation is expected to be similar for the mothers with epilepsy and for the non-epileptic controls, and will probably not affect the estimate of the actual relative risk of major congenital abnormalities.

Controversy remains whether antiepileptic drugs are the only cause of major congenital abnormalities in the offspring of women with epilepsy or whether the disease itself also plays an important role.[25, 26, 29, 30] Most studies have been small, and were not able to stratify for type of epilepsy. This made it difficult in these studies to distinguish between a teratogenic effect of the drug, and other possible explanations like a genetic trait predisposing for both epilepsy and the development of major congenital abnormalities. Some disagreement exists on whether offspring of women with epilepsy without antiepileptic drug treatment during pregnancy have an increased risk of major congenital abnormalities, but most studies including ours, did indeed not show an increased risk.[8, 16, 31] Although this suggests that epilepsy itself is not a major determinant of major congenital abnormalities, epilepsy not requiring antiepileptic drug treatment may differ from epilepsies that do need antiepileptic drug treatment.

Antiepileptic drug use in the first trimester of pregnancy was associated with a significantly increased risk of major congenital abnormalities in the offspring regardless of the type of epilepsy, suggesting a major teratogenic effect of the antiepileptic drug *per se* during organogenesis. However, offspring of women treated only in second and/or third trimester of pregnancy and not in first trimester also showed a significantly increased risk of major congenital abnormalities, primarily associated with partial epilepsy or the occurrence of seizures during first trimester. These women were not treated in the teratogenic period of embryogenesis, making it difficult to ascribe the teratogenic effect to the antiepileptic drug. There are several possible explanations for these increased risks. Firstly, we can not exclude the possibility that, due to the re-occurrence of seizures, some of these women had already restarted medication by themselves without knowledge of the treating physician. In that case the increased risk of major congenital abnormalities might be the result of antiepileptic drug teratogenesis. Secondly, the partial epilepsy in the mother and the major congenital

abnormalities in the child may be due to a common genetic predisposition. Thirdly, seizures during the first trimester of pregnancy may also be one of the causative teratogenic determinants in the development of major congenital abnormalities. When occurring during second or third trimester, seizures might even have a disruptive effect on the development of the fetus. Among women with only second and/or third trimester exposure to antiepileptic drugs, the proportion of women with seizures increased with more advanced stages of pregnancy. This may imply a yet unidentified common causative mechanism for the increase in seizure frequency and the occurrence of major congenital abnormalities in the offspring. In the 21 pregnancies with only second and/or third trimester exposure to antiepileptic drugs and the occurrence of seizures during the first trimester, two children had major congenital abnormalities. One child had postaxial polydactyly of the hand and was exposed to seizures only in first trimester. The other child had a hypertrophic pyloric stenosis and was exposed to seizures during all trimesters of pregnancy. These types of defect do not give a clue to the teratogenic mechanism involved. However, hypertrophic pylorus stenosis was observed in three children from the total maternal epilepsy cohort, of whom two had been exposed to documented third trimester maternal seizures (one also during first and second trimester).

All women with second and/or third trimester antiepileptic drug exposure had onset of epilepsy before onset of pregnancy, and during this pre-pregnancy life period, their epilepsy was usually chronically treated with antiepileptic drugs and discontinued before pregnancy. Theoretically, chronic antiepileptic drug treatment might cause damage of the maternal ovum by a direct effect or a cumulative effect, which may cause development of major congenital abnormalities in the offspring [32, 33]. In our study, however, the mean age of onset of epilepsy in women with only second and/or third trimester antiepileptic drug exposure was 18.2 years compared to a mean age of 14.1 years in women with first trimester antiepileptic drug exposure ($p = 0.0002$), and also the number of years between onset of epilepsy and age at delivery (as a measure for cumulative exposure) was lower in women with only second and/or third trimester exposure (9.1 versus 13.6 years, $p < 0.0001$), making this explanation less likely.

Our study of 4107 pregnancies suggests a teratogenic effect of antiepileptic drug treatment during pregnancy. Furthermore, it strongly suggests that, a subpopulation of women with only second and/or third trimester exposure to antiepileptic drugs are at a relatively high risk of having malformed offspring, in particularly associated with partial epilepsy or the occurrence of seizures during pregnancy.

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Chapter 5.2

Antiepileptic drug regimens and major congenital abnormalities in the offspring

5.2 Antiepileptic drug regimens and major congenital abnormalities in the offspring

Abstract

Maternal antiepileptic drug use has been associated with an increased risk of major congenital abnormalities in the offspring. To assess the risk of major congenital abnormalities associated with specific antiepileptic drug regimens, a large retrospective cohort study was performed, comprising all 1411 children of women with epilepsy and antiepileptic drug use during first trimester of pregnancy, born between 1972-1994 in 28 hospitals in four provinces in the Netherlands, and 2000 non-epileptic age and sex matched controls.

We found significantly increased risks of major congenital abnormalities for carbamazepine and valproate monotherapy, with evidence for a significant dose-response relationship for valproate. The risk of major congenital abnormalities was non-significantly increased for phenobarbital monotherapy, when caffeine co-medication was excluded. However, when caffeine was included, a significant increase in risk was found. Phenytoin monotherapy was not associated with an increased risk of major congenital abnormalities. Regarding polytherapy regimens, increased risks were found for several antiepileptic drug combinations. Clonazepam in combination with other antiepileptic drugs showed a significantly increased relative risk. Furthermore, there were significantly increased relative risks for the combination of carbamazepine and valproate and the combination of phenobarbital and caffeine with other antiepileptic drugs. Valproate +/- other antiepileptic drugs and valproate + carbamazepine were significantly associated with spina bifida and valproate +/- other antiepileptic drugs with hypospadias.

The study shows that most antiepileptic drug regimen were associated with an increased risk of major congenital abnormalities in the offspring, in particular valproate (dose-response relationship) and carbamazepine monotherapy, benzodiazepines in polytherapy, and caffeine co-medication in combination with phenobarbital.

Introduction

Antiepileptic drugs have been associated with an increased risk of major congenital abnormalities in the offspring of women using these drugs during pregnancy.[1-6] The risks of seizures during pregnancy for mother and child are well known.[7-10] Therefore, it often remains necessary to continue antiepileptic drugs during pregnancy to maintain sufficient seizure control, even if it is preferable to withdraw this medication in order to prevent the teratogenic drug effects. The risks associated with specific antiepileptic

drug regimens have not been clarified. In general, monotherapy is preferred over combination therapies,[11, 12] although not all antiepileptic drugs in monotherapy can be considered equally safe.[13-15] Teratogenic risks may also be dose-dependent. Previous studies have demonstrated a dose-response relationship for valproate[16, 17] and to a lesser extent for phenobarbital.[18] The teratogenic risk may also be different between specific polytherapy regimens and depend on specific pharmacokinetic or pharmacodynamic interactions and genetic variation in drug metabolism or at the pharmacodynamic level.[19-21] Some specific combination therapies have been shown to be teratogenic in the past, such as the combination of carbamazepine + valproate + phenobarbital +/- phenytoin and the combination of phenytoin + phenobarbital + primidone +/- other antiepileptic drugs.[18, 22] Recently, a potentiating effect of benzodiazepines on the expression of valproate induced embryopathy has been suggested.[23]

The relative risk of specific major congenital abnormalities may also differ between antiepileptic drug regimens. Associations have been found between congenital heart defects or facial clefts and phenobarbital, phenytoin or primidone,[3, 24] while carbamazepine and valproate have been associated with spina bifida aperta and hypospadias,[13, 15, 25-28] and to a lesser extent with cardiac abnormalities.[29, 30] Valproate has also been associated with skeletal defects, such as radial aplasia.[31-34]

To investigate the different risks of major congenital abnormalities associated with specific antiepileptic drug regimens, we have performed a large retrospective cohort study, comparing the offspring of antiepileptic drug treated women with the offspring of non-epileptic controls.

Methods

The study comprises offspring of women with epilepsy, with or without antiepileptic drug use during pregnancy, born between 1972-1994 in 28 hospital in four provinces of the Netherlands. Using hospital delivery books, hospital delivery registration systems, national delivery registration systems (National Perinatal Data Base LVR), outpatient clinic records for prenatal diagnosis, and obstetrical history, we aimed at ascertaining all deliveries with maternal epilepsy. In the Netherlands one third of the deliveries take place at home. Maternal epilepsy, however, is an indication for delivery at the hospital, which is recorded as reason for referral. Dysmature and premature deliveries were included, as well as stillbirths and pregnancies terminated because of severe fetal anomalies diagnosed prenatally. In total, 1348 mothers with epilepsy and 2107 children born to these women were identified. Of these 1348 women with epilepsy, 921 (1411 children) women were using antiepileptic drugs at least

during the first trimester of pregnancy. Only these were included in the analyses of this study, as this is the embryogenic period. In total, 129 different antiepileptic drug regimens were prescribed, of which 18 (14%) consisted of one antiepileptic drug, 47 (36%) of two antiepileptic drugs, 41 (32%) of three antiepileptic drugs, 15 (12%) of four antiepileptic drugs, and 8 (6%) of five antiepileptic drugs. In addition, 1955 matched non-epileptic controls and 2000 children born to these women were included in the study. Control pregnancies were matched to the cases for maternal age (± 2 years) and parity of the mother, and sex, birth year, and hospital of delivery of the child. The study protocol was approved by the Medical Ethical Committee of Erasmus University Rotterdam.

Data were collected from medical records and include general characteristics of the mother, information on pregnancy and child, obstetrical history, family history, epilepsy, medication and intoxications. The prescribed dose of the drugs was also retrieved from obstetric files, and neurologic files were requested in case of ambiguity and/or missing data. The dose used during the longest period per trimester was regarded as the total daily dose per trimester.

Endpoints of the study were major congenital abnormalities in the offspring, defined as an abnormality of an essential embryonal structure, present at birth or discovered during the first six weeks of life. Examples of major congenital abnormalities according to this definition are: neural tube defects (e.g. spina bifida aperta with/without hydrocephalus), congenital heart defects (e.g. ventricular septal defect), hypospadias, cleft lip and/or palate, pre- and/or post-axial polydactyly, club foot or congenital hip dysplasia requiring plaster therapy or surgery, and inguinal hernia requiring surgery. Information on major congenital abnormalities was completed with information from the paediatrician whenever necessary.

Data analysis

The occurrence of major congenital abnormalities in pregnancies with maternal epilepsy exposed to different drug regimens was compared to that in non-epileptic control pregnancies. Relative risks (RR) were calculated, using all non-epileptic controls as a reference. Multiple logistic regression analysis was used to adjust for putative confounding variables such as maternal age, parity, social class, sex of the child, study site, and type of epilepsy. Relative risks are presented with a 95% confidence interval (CI), which will exclude the value of 1 in case of statistical significance ($p<0.05$).

Caffeine, a drug which was previously used as adjuvant therapy for phenobarbital, was also included in the analyses, since the drug was frequently prescribed in this study population and an interaction between caffeine and antiepileptic drugs could influence the risk of major congenital abnormalities in the offspring. For this reason, caffeine is counted as one of the constituents of polytherapy regimen in the analyses. However, since previous reports did not consider caffeine as an exposure with possible relevance, data were also analyzed without taking caffeine into account.

We also tested for a dose-response relationship in monotherapies with sufficient numerators (> 1 major congenital abnormalities) and denominators (>50), using tertiles as cut-off points. The lowest tertile was used as reference.

A priori, there were several possible theories to be tested. We have focused on the following: antiepileptic drug regimens which have previously been reported to be associated with major congenital abnormalities, regimens which are frequently prescribed in this study population (n > 50), and regimens with at least one malformed offspring.

When considering specific major congenital abnormalities, we addressed the five most frequently occurring major congenital abnormalities, i.e. neural tube defects, congenital heart defects, hypospadias, polydactyly and facial clefts.

Results

Baseline characteristics of the group of women with epilepsy with first trimester exposure, and of controls are presented in table 5.2.1. There were no significant differences between the two groups. The number of children with major congenital abnormalities in the group with maternal epilepsy was 52 (3.7%) and 29 (1.5%) in the non-epileptic controls. Of the 1411 pregnancies, 899 (64%) were exposed to one antiepileptic drug, 342 (24%) to two antiepileptic drugs, 91 (6%) to three antiepileptic drugs and 25 (2%) to four antiepileptic drugs (table 5.2.2). The remaining 54 (4%) pregnancies could not be subdivided in one of the previous groups, since data on antiepileptic drug use were (partly) missing. The risks of major congenital abnormalities in offspring by the number of antiepileptic drugs are given in table 5.2.2.

The type of epilepsy did not modify the risk of major congenital abnormalities in women treated with antiepileptic drugs in the first trimester of pregnancy. The relative risk of major congenital abnormalities was similar for all groups of epilepsy: generalized (RR 3.3, CI: 1.8-5.9), partial (RR 2.4, CI: 1.3-4.4) and unknown (RR 2.2, CI 1.2-4.1).

Table 5.2.1 *Baseline characteristics of the study population.*

		Non-epileptic controls	First trimester exposure
Number of offspring:		2000	1411
Number of major congenital abnormalities in offspring:		29 (1.5%)	52 (3.7%)
Age mother:	<20	69 (4%)	43 (3%)
	20-24	484 (24%)	323 (23%)
	25-29	806 (40%)	593 (42%)
	30-34	483 (24%)	333 (24%)
	35+	158 (8%)	119 (8%)
Parity: 0		968 (48%)	648 (46%)
	1	703 (35%)	498 (35%)
	2+	329 (17%)	265 (19%)
Sex:	female	953 (47%)	697 (48%)
	male	1039 (52%)	727 (51.5%)
	unknown	8 (1%)	5 (0.5%)
Number of miscarriages:			
	0	1667 (84%)	1147 (81%)
	1	265 (13%)	184 (13%)
	2	47 (2%)	54 (4%)
	3	19 (1%)	18 (1%)
	4+	2 (0.1%)	8 (1%)

Table 5.2.2 *Relative risk (95% confidence interval) of major congenital abnormalities in offspring of women with epilepsy exposed to one or more antiepileptic drugs.*

	Treated in first trimester	
Drug combination	N (%)*	RR (95% CI)
Non-epileptic controls	29/2000 (1.5%)	1.0 (reference)
One antiepileptic drug	30/899 (3.3%)	2.4 (1.4-3.9)
Two antiepileptic drugs	16/342 (4.7%)	3.3 (1.8-6.2)
Three antiepileptic drugs	4/91 (4.4%)	3.1 (1.1-9.1)
Four or more antiepileptic drugs	2/25 (8%)	5.9 (1.3-26.3)

* Numbers are abnormalities/total exposed

Table 5.2.3 shows the risk of major congenital abnormalities for the different antiepileptic drugs in monotherapy and polytherapy. Among the monotherapies with a denominator higher than 50, the risk was significantly increased only for carbamazepine (RR 2.6, CI: 1.4-5.0) and valproate (RR 4.1, CI: 1.9-8.8), and not for phenobarbital (RR 2.0, CI: 0.8-5.3) and phenytoin (RR 0.5, CI: 0.1-3.4). When the combination of phenobarbital +/- caffeine was considered to be phenobarbital

Table 5.2.3 *Relative risk of major congenital abnormalities in offspring associated with exposure to antiepileptic drugs in monotherapy and polytherapy.*

	Monotherapy		Polytherapy	
Exposure	N (%)	RR (95% CI)	N (%)	RR (95% CI)
Barbiturates	**5/196 (3%)**	**1.8 (0.7-4.7)**	**12/302 (4%)**	**2.8 (1.4-5.6)**
phenobarbital (pb)	5/172 (3%)	2.0 (0.8-5.3)	11/276 (4%)	2.8 (1.4-5.7)
mephobarbital (mhb)	0/5 (0%)	-	2/21 (10%)	7.2 (1.6-32.2)
metharbital (mb)	-	-	0/1 (0%)	-
methylfenobarbital (mfb)	0/1 (0%)	-	-	-
primidone (prm)	0/18 (0%)	-	2/48 (4%)	3.0 (0.7-12.8)
Hydantoines	**1/151 (1%)**	**0.5 (0.1-3.4)**	**6/209 (3%)**	**2.0 (0.8-4.9)**
phenytoin (pht)	1/151 (1%)	0.5 (0.1-3.4)	6/209 (3%)	2.0 (0.8-4.9)
mephenytoin (mph)	-	-	-	-
Succinimides	**0/10 (0%)**	-	**1/35 (3%)**	**2.0 (0.3-15.1)**
ethosuximide (esx)	0/9 (0%)	-	1/33 (3%)	2.1 (0.3-16.1)
methsuximide (msx)	0/1 (0%)	-	0/2 (0%)	-
Benzodiazepines	**0/25 (0%)**	-	**6/106 (6%)**	**4.1 (1.7-10.1)**
bromazepam (bzp)	0/1 (0%)	-	0/1 (0%)	-
clobazam (clm)	0/4 (0%)	-	1/27 (4%)	2.6 (0.3-19.9)
chloordiazepoxide (cdp)	-	-	0/7 (0%)	-
clonazepam (clp)	0/9 (0%)	-	4/31 (13%)	10.1 (3.3-30.6)
diazepam (dzp)	0/7 (0%)	-	1/27 (4%)	2.6 (0.3-19.9)
flurazepam (flp)	-	-	0/1 (0%)	-
lorazepam (lzp)	0/1 (0%)		0/5 (0%)	-
nitrazepam (nzp)	-		0/4 (0%)	-
oxazepam (ozp)	0/3 (0%)	-	0/5 (0%)	-
temazepam (tzp)	-	-	0/2 (0%)	-
Tricyclics	**14/378 (4%)**	**2.6 (1.4-5.0)**	**12/225 (5%)**	**3.8 (1.9-7.6)**
carbamazepine (cbz)	14/376 (4%)	2.6 (1.4-5.0)	11/222 (4%)	3.5 (1.7-7.2)
oxcarbazepine (oxc)	0/2 (0%)	-	1/3 (33%)	34.0 (3.0-386.0)
Other antiepileptic drugs				
trimethadion (tmd)	-	-	1/5 (20%)	17.0 (1.8-157.0)
beclamide (bcl)	-	-	0/1 (0%)	-
acetazolamide (aca)	1/1 (100%)	-	0/4 (0%)	-
valproate (vpa)	9/158 (6%)	4.1 (1.9-8.8)	8/136 (5%)	3.7 (1.6-8.6)
vigabatrine (vgb)	-	-	0/1 (0%)	-
sultiame (sul)	0/1 (0%)	-	0/2 (0%)	-
Other drugs				
caffeine (caf)	-	-	5/75 (7%)	4.9 (1.8-12.9)

monotherapy, the risk of major congenital abnormalities became significantly increased (RR 2.6, CI: 1.1-6.0). The relative risks of major congenital abnormalities for many of the polytherapy regimens were increased, including barbiturates, benzodiazepines, tricyclics, valproate and caffeine. Again, when considering the combination of phenobarbital + other antiepileptic drugs +/- caffeine, a significantly increased risk of major congenital abnormalities was found (RR 2.5, CI: 1.2-5.3), in contrast to the non-significant finding for phenobarbital + other antiepileptic drugs - caffeine (RR 2.0, CI: 0.8-4.8). The relative risk of major congenital abnormalities for the offspring exposed to the combination phenobarbital + other antiepileptic drugs + caffeine was 5.1 (CI: 1.5-17.4).

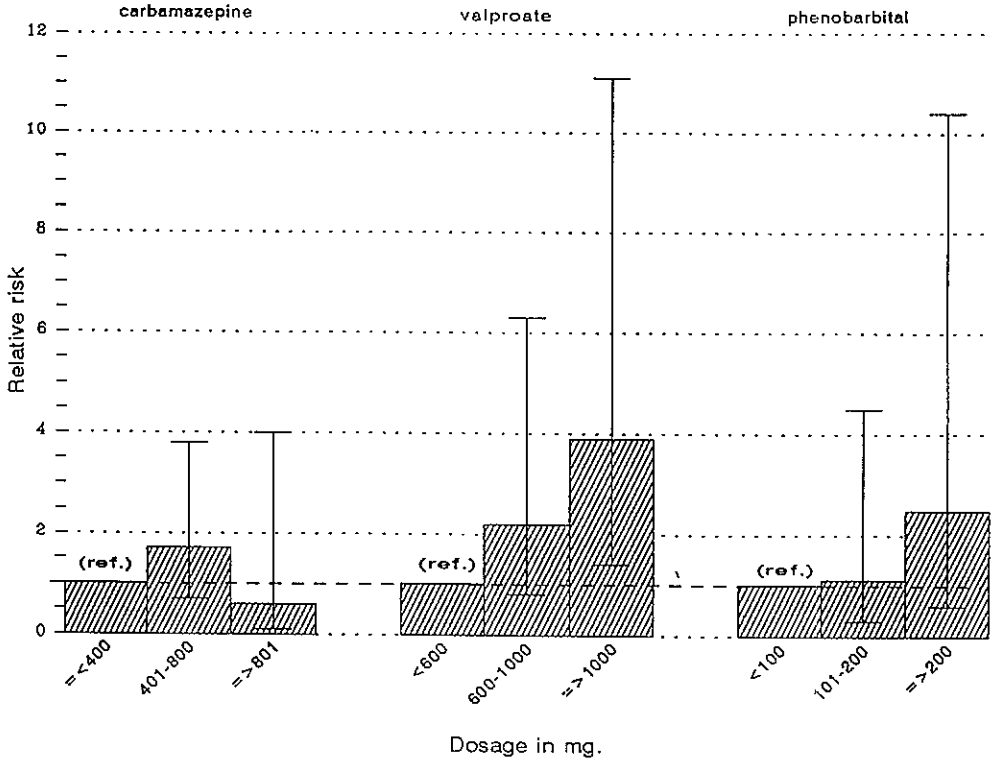

Figure 5.2.1 *Risk of major congenital abnormalities by increasing dose of the drug regimen in monotherapy (cut-off point at 33.3% and 66.6%). Above the bars, the upper limit for the 95% confidence interval is given.*

For the monotherapies phenobarbital, carbamazepine and valproate, the number of informative pregnancies was large enough to allow testing for a dose-response relationship (figure 5.2.1). We found a dose-response relationship for phenobarbital and valproate, which was only significant for the highest dose of valproate. Offspring of women receiving valproate ≥ 1000 mg/day had a significantly increased risk of major congenital abnormalities compared to women receiving < 600 mg/day (RR 3.9, CI: 1.4-11.1). Offspring of women receiving phenobarbital ≥ 200 mg/day had a non-significantly increased risk of major congenital abnormalities compared to women receiving < 100 mg/day (RR 2.5, CI: 0.6-10.4).

In table 5.2.4 all antiepileptic drug regimens with at least one malformed offspring are shown. There were no children with major congenital abnormalities exposed to the combination of phenobarbital + phenytoin + primidone +/- other antiepileptic drugs or the combination of carbamazepine + phenobarbital + valproate +/- phenytoin.

Table 5.2.4 *Proportion of major congenital abnormalities in offspring associated with exposure to specific drug regimens. All regimens with at least one malformed offspring.*

Antiepileptic drug regimen	First trimester exposure	
	N	%
cbz+caf+mbh+pb+pht	1/2	
cbz+caf+pb+pht+vpa	1/1	
clp+pb+pht	1/2	
caf+pb+pht	1/22	(4%)
cbz+pht+vpa	1/4	
clm+oxc+vpa	1/1	
caf+pb	2/19	(11%)
cbz+dzp	1/9	
cbz+clp	1/8	
clp+esx	1/1	
cbz+mhb	1/3	
cbz+vpa	4/58	(5%)
clp+vpa	1/6	
pb+prm	2/14	(13%)
pb+tmd	1/1	
pb+pht	1/67	(2%)
cbz+pb	1/39	(3%)
cbz	14/376	(4%)
pb	5/172	(3%)
pht	1/151	(1%)
vpa	9/158	(6%)
aca	1/1	

Abnormalities occurring more than two times are summarized in table 5.2.5, with type of epilepsy of the mother and antiepileptic drug exposure. When considering specific major congenital abnormalities, we addressed the five major groups (not in table). Significant associations were found between neural tube defects and valproate +/- other antiepileptic drugs (RR 5.4, p=0.004), valproate - other antiepileptic drugs (RR 4.0, p=0.03) and valproate + carbamazepine (RR 8.1, p=0.01), and between hypospadias and valproate +/- other antiepileptic drugs (RR 4.8, p=0.03) and valproate - other antiepileptic drugs (RR 4.8, p=0.05).

Discussion

Our study shows a significantly increased risk of major congenital abnormalities for carbamazepine and valproate monotherapy, with evidence for a significant dose-response relationship for valproate. The risk of major congenital abnormalities was non-significantly increased for phenobarbital monotherapy, when caffeine co-medication was excluded. However, when caffeine was included, a significant increase in risk was found. Phenytoin monotherapy was not associated with an increased risk of major congenital abnormalities. Regarding polytherapy regimens, increased risks were found for several antiepileptic drug combinations. Clonazepam in combination with other antiepileptic drugs showed a significantly increased relative risk. Furthermore, there was a significantly increased relative risk for the combination of carbamazepine and valproate and the combination of phenobarbital and caffeine with other antiepileptic drugs. Valproate +/- other antiepileptic drugs and valproate + carbamazepine were significantly associated with spina bifida and valproate +/- other antiepileptic drugs with hypospadias.

As our study is based on medical records, and therefore for a proportion of women data on a number of variables, such as time of treatment and dose of antiepileptic drugs, were not available. Some of the available pregnancies could therefore not be included in the analyses. Since only obviously visible defects could be included, the frequency of congenital abnormalities in this study may most likely be an underestimate of the actual frequency. However, this underestimation is expected to be similar for the mothers with epilepsy and for the non-epileptic controls, and will probably not affect the estimate of the actual relative risk of major congenital abnormalities. This is especially relevant for a number of heart defects, urogenital abnormalities and others. A major advantage of our approach is the population-based design.

Previous follow-up studies have shown a higher risk of major congenital abnormalities associated with antiepileptic drug in polytherapy than antiepileptic drug in monotherapy.[11, 12, 19, 33, 35, 36] However, the risk of major congenital abnormalities associated with specific antiepileptic drug regimens have been shown to be higher. Strong associations have been found for valproate and/or carbamazepine with spina bifida aperta and hypospadias[13, 15, 25-28] and for carbamazepine also with cardiac abnormalities,[29, 30] while phenobarbital, phenytoin or primidone have been associated with congenital heart defects or facial clefts.[3, 24] Valproate has also been associated with skeletal defects, such as radial aplasia.[31-34] Also previous studies have demonstrated a dose-response relationship for valproate.[16, 17]

Table 5.2.5 *Major congenital abnormalities occurring more than two times, type of epilepsy and dose of antiepileptic drugs in milligrams.*

Major congenital abnormalities	Epilepsy	CBZ	VPA	PHT	PB	OTH
Congenital heart defects (n=11)						
Transposition Great Arteries	P				150	
SVT, enlarged RA/V Cava Sup	G	600				
Ventricular septal defect[a]	G		2400			
Ventricular septal defect[b]	G	600				
Cardiomyopathy[c]	P			300	225	1.5[1]
Congenital heart defect[d]	G		600			
Congenital heart defect[e]	P				250	
Pulmonalis stenosis	P	600				
Wolf-Parkinson-White	U	200				
Fallot tetralogy	G	600				
Congenital heart defect[f]	U				200	500[2]
Neural tube defects (n=12)						
Spina bifida aperta[a]	G		2400			
Spina bifida aperta + hydroceph	P	600	1500			
Spina bifida aperta[g]	U	800	1500			
Spina bifida aperta	G		1500			
Spina bifida aperta + hydroceph	G		1500			
Spina bifida aperta + hydroceph	U	800				
Anencephaly	U				150	900[3]
Spina bifida cystica[h]	P		1800			3000[4]/22[5]
Hydrocephalus	P	800	1500			
Sacrumdefect[i]	G			400		
Hydrocephalus[j]	G	200				
Spina bifida occulta[f]	U				200	500[2]
Hypospadias (n=8)						
Hypospadias[k]	P	600				
Hypospadias[i]	G			400		
Hypospadias	P	400				
Hypospadias	G		1200			
Hypospadias	P		800			
Hypospadias	G		600			
Hypospadias	P	600				

Table 5.2.5 *Continued....*

Major congenital abnormalities	Epilepsy	CBZ	VPA	PHT	PB	OTH
Hypospadias	G	600	300	80	270	180[6]
Polydactylies (n=6)						
Polydactyly	P			150	150	150[6]
Preaxial polydactyly	U		500			
Polydactyly	U	100	900	200		
Polydactyly	G	400				
Preaxial polydactyly[l]	U	300				
Polydactyly[m]	G		1500			3[1]
Cleft lip and/or palate (n=4)						
Cleft lip	P				225	75[6]
Cleft lip[i]	G			400		
Cleft lip	P				250	
Cleft lip	G	400				

CBZ = carbamazepine, VPA = valproate, PHT = phenytoin, PB = phenobarbital, OTH = others (dose in milligrams)

Type of epilepsy: G = generalized epilepsy
P = partial epilepsy
U = unknown

Patients with more than one defect, listed among the four defects with highest frequency:

a: one patient with spina bifida aperta and ventricular septal defect
b: one patient with ventricular septal defect and microcephaly
c: one patient with cardiomyopathy and adrenal gland haemorrhage
d: one patient with congenital heart defect and inguinal hernias
e: one patient with congenital heart defect and de novo aberrant chromosome 2
f: one patient with spina bifida occulta, congenital heart defect, anal atresia and oesophageal atresia (partial VACTERL association)
g: one patient with spina bifida aperta an microcephaly
h: one patient with spina bifida cystica and clubfoot
i: one patient with sacrumdefect, hypospadias and cleft lip
j: one patient with hydrocephalus, thymus atrophy, growth retardation, single umbilical artery and liver insufficiency
k: one patient with hypospadias and diastasis recti
l: one patient with preaxial polydactyly and syndactyly
m: one patient with polydactyly, radial aplasia, clenching fingers and spine abnormalities

1: clonazepam
2: primidone
3: trimethadion
4: oxcarbazepine
5: clobazam
6: caffeine

For some of the antiepileptic drugs in polytherapy it remains difficult to attribute the risk of major congenital abnormalities to one or more specific combinations (see table 5.2.3 and 5.2.4). Phenobarbital, for example, was prescribed in several different combinations, and two of the 11 children with major congenital abnormalities in this group were even exposed to five antiepileptic drugs at once. Seven of 11 children with major congenital abnormalities exposed to carbamazepine polytherapy were exposed to a combinations of carbamazepine + valproate with or without other antiepileptic drugs, of which 3 children developed a spina bifida.

Our study suggests an increased risk of major congenital abnormalities associated with benzodiazepines in combination with other antiepileptic drugs. Two affected children had been exposed to a benzodiazepine in combination with carbamazepine (carbamazepine + clonazepam and carbamazepine + diazepam) and two in combination with valproate (valproate + clonazepam and valproate + oxcarbazepine + clobazam). The combination of valproate with a benzodiazepine has previously been reported as having a possible potentiating effect regarding the risk of major congenital abnormalities [23]. It is important to note that the risk of major congenital abnormalities associated with these combinations may mainly be due to carbamazepine or valproate, which by themselves are teratogenic. However, the relative risks of the combinations were much higher, and with benzodiazepine monotherapy (n = 25) no adverse congenital effects were observed, suggesting an additive or potentiating effect of the combination therapy.

Five children with major congenital abnormalities were exposed to caffeine in polytherapy, of whom all five were exposed to this drug in combination with phenobarbital with or without another antiepileptic drug. Caffeine alone or in combination with phenobarbital has not previously been associated with major congenital abnormalities [37-41]. However, caffeine exposure has never been analyzed in the context of antiepileptic drug induced teratogenesis. We can not exclude that the teratogenic effect of caffeine in polytherapy is explained by the phenobarbital medication, but also a specific metabolic interaction remains possible.

Our study shows that antiepileptic drugs in polytherapy are more often associated with an increased risk of major congenital abnormalities than monotherapies, and in general the risks associated with polytherapy are higher. Valproate and carbamazepine monotherapy show a significantly increased risk of major congenital abnormalities. Valproate monotherapy is especially associated with spina bifida and hypospadias. If valproate is prescribed in monotherapy, keeping the total daily dose as low as possible might diminish the risk of major congenital abnormalities, given the dose-response

relationship observed in this and previous studies. Additionally, our study shows that the combination of benzodiazepines with other antiepileptic drugs, especially valproate and carbamazepine, is associated with an increased risk of major congenital abnormalities and is therefore perhaps better to be avoided. Finally, our findings argue against the prescription of the combination of caffeine and phenobarbital. Caffeine has always been considered as a harmless drug, mainly prescribed to diminish the sedative effect barbiturates, but in our study it was associated with a significantly increased risk of major congenital abnormalities. For the evaluation of total caffeine exposure during pregnancy, one has to take into account that a majority of pregnant women have an aversion against coffee during a variable period in first trimester of pregnancy. This would lead to lower caffeine intake in this period of embryogenesis, but would be circumvented if caffeine is prescribed as co-medication for phenobarbital. We can not, of course, exclude that caffeine is a risk indicator for patients predisposed to phenobarbital side-effects, for which caffeine is prescribed. An important point in future research will be the effect of dietary caffeine (coffee, cola) or other caffeine medication (e.g. aspirin) on the risk of major congenital abnormalities in antiepileptic drug users.

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Chapter 5.3

Maternal epilepsy, antiepileptic drugs and fetal growth

5.3 Maternal epilepsy, antiepileptic drugs and fetal growth

Abstract

To study the influence of antiepileptic drugs and epilepsy on fetal growth in the offspring of women with epilepsy, a retrospective cohort study was performed, comprising all offspring of women with epilepsy born between 1972-1994 in 28 hospitals in four provinces in the Netherlands. Data were available for 1605 children of women with epilepsy exposed to antiepileptic drugs during pregnancy, 421 children of women with epilepsy not exposed to antiepileptic drugs, and 2000 non-epileptic age and sex matched control offspring. The main outcome measures were fetal growth assessed by weight, length and head circumference at birth, placental weight and perinatal status of the child assessed by Apgar scores.

Offspring of mothers with epilepsy using antiepileptic drugs during the first trimester of pregnancy had significantly lower weight, were shorter and had smaller head circumference at birth compared to non-epileptic controls. Valproate monotherapy was associated with lower Apgar scores and valproate polytherapy was associated with lower weight. Carbamazepine was associated with lower weight, shorter length, and smaller head circumference. Phenobarbital was associated with lower weight and smaller head circumference. Lower weight and smaller head circumference were also associated with generalized epilepsy and seizure occurrence during first trimester of pregnancy. When stratifying for type of epilepsy within the mono- or polytherapy regimens, we found an additive effect of the combination generalized epilepsy and valproate, carbamazepine, or phenobarbital on head circumference, and of generalized epilepsy in combination with valproate on weight.

Our study shows that antiepileptic drugs as well as the underlying epilepsy appear to play an important role in growth and development of the fetus.

Introduction

Several studies have been performed to assess the risk of major congenital abnormalities in the offspring of women with epilepsy[1-16], and most of these studies showed a two- to threefold increased risk of major congenital abnormalities in the offspring associated with antiepileptic drug use during pregnancy compared to the general population. In addition to major congenital abnormalities, minor anomalies and psychomotor development, growth is also an important endpoint of teratogenesis. Only a limited number of studies have evaluated growth impairment or adverse perinatal outcome in association with epilepsy and antiepileptic drug treatment during pregnancy. Findings of these studies have been contradictory. Some studies showed impairment

of all growth parameters and/or lower Apgar scores,[9, 17-21] some found an association with only one of these parameters,[12, 22-25] and others showed growth impairment to be associated with specific antiepileptic drugs such as valproate,[17, 26] carbamazepine[8] and phenobarbital [17, 27, 28]. One study found an association between seizures and low birth weight.[29] Finally, a number of studies did not find any associations between antiepileptic drugs and growth impairment or adverse perinatal outcome.[30-32] We have performed an extensive retrospective population-based cohort study, with the aim of assessing the risks of adverse perinatal outcome and growth impairment associated with maternal epilepsy and antiepileptic drug treatment during pregnancy.

Methods

The study comprised offspring of women with epilepsy, with or without antiepileptic drug use during pregnancy, born between 1972-1994 in 28 hospital in four provinces of the Netherlands. Using hospital delivery books, hospital delivery registration systems, national delivery registration systems (National Perinatal Data Base LVR), outpatient clinic records for prenatal diagnosis, and obstetrical history, we aimed at ascertaining all deliveries with maternal epilepsy independent of outcome, including pregnancies terminated after prenatal diagnosis. Dysmature and premature deliveries were included, as well as stillbirths and pregnancies terminated because of severe fetal anomalies diagnosed prenatally. Included in the study are 1348 mothers with epilepsy and 2107 children born to these women, as well as 1955 matched non-exposed controls and 2000 children born to these women. Control pregnancies were matched to the exposed pregnancies for maternal age (+/- 2 years) and parity, and sex, year of birth and hospital of delivery of the child. The study protocol was approved by the Medical Ethical Committee of Erasmus University.

Data collected from medical records included general characteristics of the mother, information on pregnancy and child, obstetrical history, family history, epilepsy, medication and intoxications. Information on type of epilepsy was retrieved from obstetric or neurologic patient files or from correspondence with treating neurologists. Epilepsy of the mother was classified into generalized, partial or unknown.

Endpoints of the present study were birth weight, length and head circumference, placental weight, and Apgar scores at one and five minutes. This information was retrieved from patient files and sometimes completed with information from the paediatrician.

The mothers with epilepsy were divided into five exposure groups. Group I *(first trimester exposure)* includes women using antiepileptic drugs at least during the first

trimester of pregnancy (921 women and 1411 children). Group II *(only second/third trimester exposure)* includes women who were only treated with antiepileptic drugs during the second and/or third trimester (79 women and 115 children). Each of the women with second and/or third trimester antiepileptic drug use had onset of epilepsy before pregnancy and were on chronic antiepileptic drug medication, which was discontinued before pregnancy. Group III *(unknown trimester)* includes women who were using antiepileptic drugs in pregnancy, without documentation in which trimester (54 women and 79 children). Group IV *(non-exposed epileptic)* includes women without antiepileptic drug use throughout pregnancy (244 women and 421 children). For 50 (3.5%) women with epilepsy (81 children) no documentation of antiepileptic drug use during pregnancy could be retrieved and this group was therefore not included in the analyses.

Data analysis

Mean birth weight, length and head circumference and placental weight were calculated. Linear regression analysis was used to adjust for putative confounding variables such as sex of the child and weeks of gestation, and 95% confidence intervals (CI) of the difference of the means were calculated. Apgar scores at one and five minutes were divided into two groups and multiple logistic regression was used to calculate the relative risk (RR) of a score ≤6 compared to a score >6, adjusted for weeks of gestation. For this analysis, pregnancies terminated prenatally were excluded. Relative risks are presented with 95% confidence intervals (CI), which will exclude the value 1 in case of statistical significance.

We performed four analyses stratifying the offspring by the following characteristics:

1. the maternal exposure groups (I-IV) versus the non epileptic controls;
2. the three different types of maternal epilepsy (generalized, partial and unknown), adjusting for the variables described above as well as the exposure groups (I-IV);
3. occurrence of maternal seizures versus no occurrence of maternal seizures during pregnancy, adjusting for the variables above as well as the exposure groups (I-IV);
4. prenatal exposure to the major antiepileptic drugs in mono- or polytherapy.

When significant differences of any parameter were found for specific antiepileptic drugs, we tested for a dose-response relationship.

Results

Antiepileptic drug exposure by trimester

Baseline characteristics are presented in table 5.3.1. No significant differences were found between the four exposure groups (I-IV) regarding age, parity, social class, sex of the child and miscarriages. The results of the analysis based on antiepileptic drug treatment during the three trimesters in pregnancy are shown in table 5.3.2. The offspring of group I *(first trimester exposure)*, compared to the offspring of the control group, had a significantly lower mean birth weight (mean adjusted difference (d) = 44 g, CI: 10.6-77.4, p=0.01), lower length (d = 0.3 cm, CI: 0.05-0.5, p=0.005) and smaller head circumference (d = 0.6 cm, CI: 0.4-0.8, p<0.0001). The offspring of group II *(only second/third trimester exposure)* had a significantly smaller head circumference (d = 0.8 cm, CI: 0.1-1.5, p=0.02), while placental weight was found to be higher (d = 34 g, CI: 5-63, p=0.02). In group III *(unknown trimester)*, a relatively small group, no significant differences were found, although length and head circumference tended to be reduced. The offspring of group IV *(non-exposed epileptic)* had a significantly higher weight compared to the non-epileptic controls (d = 53 g, CI: 1.7-104, p=0.04). Placental weight in this group also tended to be higher.

Type of epilepsy and occurrence of seizures during pregnancy

The results of the second analysis, in which the three different types of epilepsy were compared, are shown in table 5.3.3. Compared to the offspring of non-epileptic controls, we found a significantly lower weight for offspring of women with generalized epilepsy (d = 78 g, CI: 31-124, p=0.0003) and unknown type of epilepsy (d = 68 g, CI: 25-111, p=0.001). A significantly lower length (d = 0.5 cm, CI: 0.2-0.9, p=0.01) was found only for the offspring of women with generalized epilepsy. Head circumference was significantly smaller for offspring of all types of epilepsy (generalized: d = 1.0 cm, CI: 0.6-1.4, p<0.0001, partial: d = 0.4 cm, CI: 0.1-0.7, p=0,01 and unknown: d = 0.7 cm, CI: 0.4-1.0, p=0.0001). Placental weight was significantly lower for offspring of women with unknown type of epilepsy (d = 28 g, CI: 15-41, p<0.0001). When comparing only by type of maternal epilepsy, we found a significantly lower weight (d = 59 g, CI: 0.4-118, p=0.03) and smaller head circumference (d = 0.6 cm, CI: 0.2-1.0, p=0.05) for offspring of mothers with generalized epilepsy compared to mothers with partial epilepsy, and a significantly lower placental weight for offspring of mothers with unknown type of epilepsy

Table 5.3.1 *Baseline characteristics of the study population.*

	Controls	Group I (first trimester exposure)	Group II (only second/third trimester exposure)	Group III (unknown trimester)	Group IV (non-exposed epileptic)
Number pregnancies	2000	1411	115	79	421
Age:					
<20	69 (4%)	43 (3%)	3 (3%)	7 (9%)	24 (6%)
20-24	484 (24%)	323 (23%)	34 (29%)	14(18%)	99 (24%)
25-29	806 (40%)	593 (42%)	48 (42%)	34(43%)	160 (38%)
30-34	483 (24%)	333 (24%)	23 (20%)	17(23%)	98 (23%)
35+	158 (8%)	119 (8%)	7 (6%)	7(9%)	40 (9%)
Parity:					
0	968 (48%)	648 (46%)	54 (47%)	38 (48%)	171 (41%)
1	703 (35%)	498 (35%)	44 (38%)	27 (34%)	156 (37%)
2+	329 (17%)	265 (19%)	17 (15%)	14 (18%)	94 (22%)
Sex:					
female	953 (47%)	697 (48%)	53 (46%)	31 (39%)	203 (48%)
male	1039 (52%)	727 (51.5%)	62 (54%)	48 (61%)	218 (52%)
unknown	8 (1%)	5 (0.5%)	0 (0%)	0 (0%)	0 (0%)
Miscarriage:					
0	1667 (84%)	1147 (81%)	99 (86%)	64 (81%)	341 (81%)
1	265 (13%)	184 (13%)	13 (11%)	10 (13%)	68 (16%)
2	47 (2%)	54 (4%)	3 (3%)	3 (4%)	6 (1.5%)
3+	21 (1%)	26 (2%)	0 (0%)	2 (2%)	6 (1.5%)
Maternal epilepsy:					
generalized	-	413 (29%)	35 (31%)	20 (25%)	88 (21%)
partial	-	520 (37%)	43 (37%)	19 (24%)	124 (29%)
unknown	-	478 (34%)	37 (32%)	40 (51%)	209 (50%)

Table 5.3.2 *Growth parameter and Apgar scores at one and five minutes for the four exposure groups and the non-epileptic controls.*

		Controls	Group I (first trimester exposure)	Group II (only second/third trimester exposure)	Group III (unknown trimester)	Group IV (non-exposed epileptic)
	N	1971	1383	113	76	414
Weight	mean	3243	3199*	3192	3236	3296*
(grams)	se	10.9	13.0	45.6	55.6	23.8
	N	1079	766	57	32	234
Length	mean	49.7	49.4*	49.2	49.0	49.6
(cm)	se	0.08	0.10	0.35	0.47	0.17
	N	696	458	35	16	124
Head circumference	mean	34.6	34.0*	33.8*	33.7	34.4
(cm)	se	0.08	0.09	0.34	0.51	0.18
	N	1682	1196	94	54	356
Placenta	mean	565	555	599*	572	579
(cm)	se	3.4	4.0	14.4	19.0	7.4
Apgar score 1 minute	≤6	189 (10%)	153 (12%)	11 (10%)	8 (11%)	36 (9%)
(score 1-10)	>6	1721 (90%)	1185 (88%)	101 (90%)	56 (89%)	372 (91%)
RR (95% CI)			1.1 (0.9-1.4)	0.7 (0.3-1.5)	0.7 (0.5-1.1)	1.1 (0.5-2.3)
Apgar score 5 minutes	≤6	54 (3%)	59 (5%)	4 (4%)	5 (7%)	16 (4%)
(score 1-10)	>6	1829 (97%)	1251 (95%)	107 (96%)	67 (93%)	381 (96%)
RR (95 % CI)			1.4 (0.9-2.2)	0.4 (0.1-2.0)	0.9 (0.4-1.8)	2.6 (0.9-7.3)

* = significantly different from non-epileptic controls

Table 5.3.3 *Growth parameters and Apgar scores at one and five minutes for the three types of maternal epilepsy.*

		Group I-IV		
		Generalized	Partial	Unknown
	N	546	590	750
Weight	mean	3165*,**	3224	3175*
(grams)	se	22.2	20.1	20.8
	N	276	378	435
Length	mean	49.2*	49.4	49.4
(cm)	se	0.17	0.15	0.15
	N	170	229	234
Head circumference	mean	33.6*,**	34.2*	33.9*
(cm)	se	0.17	0.15	0.16
	N	472	596	632
Placenta	mean	568	557	537*,***
(cm)	se	6.9	6.2	6.5
Apgar score 1 minute	≤6	62 (12%)	69 (10%)	89 (12%)
	>6	472 (88%)	625 (90%)	679 (88%)
Apgar score 5 minutes	≤6	30 (6%)*,**	26 (4%)	35 (5%)
	>6	498 (94%)	666 (96%)	710 (95%)

* = significantly different from the non-epileptic controls (measures presented in table 5.3.2)
** = significantly different from partial epilepsy
*** = significantly different from generalized and partial epilepsy

compared to women with generalized epilepsy (d = 31 g, CI: 12-50, p<0.0001) and compared to women with partial epilepsy (d = 20 g, CI: 2-38, 0.01). Offspring of women with generalized epilepsy had a significantly increased risk of an Apgar score ≤ 6 at five minutes compared to non-epileptic controls (RR = 1.9, CI: 1.1-3.2) and compared to offspring of women with partial epilepsy (RR = 1.9, CI: 1.0-3.7). None of the other outcome measures was significantly associated with type of epilepsy.

The third analysis, in which each of the outcome measures was compared between offspring of women with and without seizures during pregnancy, showed a significantly smaller head circumference for offspring of mothers with seizures during first trimester of pregnancy (d = 0.6 cm, CI: 0.1-1.1, p=0.04), compared to women without seizures during first trimester (not shown in table). We did not find any difference in outcome when considering seizures during second or third trimester.

Antiepileptic drug regimens

Since significant results from the first analysis were found consistently in group I and the other groups consisted of relatively small numbers, for the analysis of the four major antiepileptic drugs we focused on group I only (table 5.3.4). For valproate monotherapy we found significantly increased risk of an Apgar score ≤6 at one minute (RR = 1.8, CI: 1.1-2.9) and at five minutes (RR = 2.5, CI: 1.1-5.3), compared to non-epileptic controls. For valproate polytherapy we found a significantly lower weight compared to non-epileptic controls (d = 93 g, CI: 8-178, p=0.02) and compared to valproate in monotherapy (d = 121 g, CI: 10-232, p=0.03), a significantly lower placental weight compared to non-epileptic controls (d = 29 g, CI: 2-56, p=0.03) and compared to valproate in monotherapy (d = 41 g, CI: 5-77, p=0.03), and a significantly lower head circumference (d = 0.9, CI: 0.3-1.5, p=0.002) compared to non-epileptic controls.

Compared to non-epileptic controls we found a significantly shorter length (d = 0.8 cm, CI: 0.4-1.2, p=0.0002) and smaller head circumference (d = 0.8 cm, CI: 0.4-1.2, p<0.0001) for carbamazepine monotherapy, and a significantly lower weight (d = 86 g, CI: 18-154, p=0.02) and smaller head circumference (d = 1.2 cm, CI: 0.7-1.7, p<0.0001) for carbamazepine polytherapy. A significantly smaller head circumference (d = 0.9 cm, CI: 0.3-1.5, p=0.001) was found for phenobarbital monotherapy, and a significantly lower weight (d = 111 g, CI: 50-172, p=0.0001), smaller head circumference (d = 0.7 cm, CI: 0.2-1.2, p=0.004), and lower placental weight (d = 36 g, CI: 17-55, p=0.0001) for phenobarbital polytherapy. Phenytoin in mono- or polytherapy was not associated with any of the outcome measures.

Table 5.3.4 *Growth parameters and Apgar scores at one and five minutes for the four major antiepileptic drugs.*

		Valproate		Carbamazepine		Phenytoin		Phenobarbital	
		Mono	Poly	Mono	Poly	Mono	Poly	Mono	Poly
	N	158	134	365	217	148	203	168	272
Weight	mean	3271	3150*,**	3217	3157*	3272	3211	3191	3132*
(grams)	se	38.3	41.6	25.5	33.1	40.0	34.1	37.5	29.5
	N	77	75	190	115	84	127	111	162
Length	mean	49.7	49.4	48.9*	49.2	49.8	49.8	49.5	49.3
(cm)	se	0.30	0.30	0.19	0.25	0.28	0.23	0.24	0.20
	N	42	47	129	70	55	63	57	77
Head circumference	mean	34.4	33.7*	33.8*	33.4*	34.7	34.3	33.7*	33.9*
(cm)	se	0.29	0.27	0.16	0.22	0.25	0.23	0.28	0.24
	N	125	113	313	187	133	183	151	234
Placenta	mean	577	536*,**	572	547	562	547	546	529*
(grams)	se	12.6	13.2	8.0	10.3	12.3	10.4	11.4	9.2
Apgar score 1 minute	≤6	26 (17%)	16 (14%)	36 (10%)	26 (13%)	18 (13%)	22 (11%)	14 (8%)	22 (9%)
(score 1-10)	>6	126 (83%)	108 (86%)	321 (90%)	183 (87%)	126 (87%)	173 (89%)	153 (92%)	236 (91%)
RR (95% CI)		1.8 (1.1-2.9)	1.5 (0.8-2.5)	0.8 (0.6-1.3)	1.3 (0.9-2.1)	1.1 (0.6-1.9)	1.1 (0.7-1.8)	0.8 (0.5-1.5)	0.8 (0.5-1.3)
Apgar score 5 minutes	≤6	10 (7%)	6 (7%)	14 (4%)	10 (5%)	5 (3%)	13 (5%)	5 (3%)	11 (6%)
(score 1-10)	>6	141 (93%)	115 (93%)	339 (96%)	194 (95%)	140 (97%)	323 (95%)	154 (97%)	176 (94%)
RR (95% CI)		2.5 (1.2-5.3)	2.2 (0.9-5.3)	0.9 (0.4-1.9)	2.0 (1.0-4.1)	0.5 (0.1-2.1)	2.2 (1.1-4.6)	1.1 (0.4-3.1)	1.9 (0.9-3.7)

* = significantly different from the non-epileptic controls
** = significantly different from monotherapy

We tested for a dose-response relationship for those monotherapies for which a growth parameter or perinatal outcome parameter was found to be significantly different from the non-epileptic controls, being apgar score at one and five minutes with valproate, length and head circumference for carbamazepine, and head circumference for phenobarbital. We found evidence for a dose-response relationship only for the association between phenobarbital and head circumference. The mean head circumferences of offspring of women receiving phenobarbital < 100 mg/day, 100- 200 mg/day, and ≥ 200 mg/day, were 35.2 cm, 33.9 cm, and 30,7 cm respectively.

Interaction between antiepileptic drugs and maternal factors

Since weight, head circumference, and placental weight were significantly associated with several types of epilepsy compared to non-epileptic controls and also compared to each other (second analysis) we also stratified for type of epilepsy within the four major antiepileptic drugs in mono- or polytherapy. These analyses were limited to those growth- or perinatal outcome parameters which were found to be significantly different from the non-epileptic controls. We found evidence for interaction between generalized epilepsy and valproate polytherapy on weight (3067 g for the combination valproate polytherapy users with generalized epilepsy versus 3150 g for valproate polytherapy and 3188 g for generalized epilepsy) and head circumference (32.9 cm for the combination versus 33.7 cm for both separately). We also found evidence for interaction between valproate polytherapy and unknown type of epilepsy on placental weight (492 g for the combination valproate polytherapy users with unknown epilepsy versus 536 g for valproate polytherapy and 537 g for unknown epilepsy) No evidence for interaction was found for Apgar scores. For head circumference we found evidence for interaction between generalized epilepsy and carbamazepine monotherapy (33.0 cm for the combination versus 33.4 cm for carbamazepine monotherapy and 33.7 cm for generalized epilepsy), and between generalized epilepsy and carbamazepine polytherapy (33.4 for the combination versus 33.9 cm for carbamazepine polytherapy and 33.7 for generalized epilepsy). Furthermore, for weight we found evidence for interaction between carbamazepine and partial epilepsy (3133 for the combination versus 3157 cm for carbamazepine polytherapy and 3224 for partial epilepsy) and between carbamazepine polytherapy and unknown epilepsy (3095 for the combination versus 3157 cm for carbamazepine polytherapy and 3175 for unknown epilepsy). Finally, we also found this evidence for interaction between phenobarbital monotherapy and generalized epilepsy on head circumference (32.4 cm for the combination versus 33.7 for both separately).

Discussion

Our study shows that offspring of women with epilepsy using antiepileptic drugs during pregnancy had significantly lower weight, shorter length and smaller head circumference compared to non-epileptic controls. Lower weight and smaller head circumference were also associated with generalized epilepsy and seizure occurrence during the first trimester of pregnancy (only head circumference). Offspring of women using valproate monotherapy during first trimester of pregnancy had significantly lower Apgar scores than non-epileptic controls and valproate polytherapy was associated with a significantly decreased weight and placental weight. Carbamazepine monotherapy was associated with a significantly shorter length and smaller head circumference, while carbamazepine polytherapy was associated with a significantly lower weight and smaller head circumference. Phenobarbital monotherapy was associated with a significantly smaller head circumference, and phenobarbital polytherapy was associated with a significantly lower weight, smaller head circumference, and lower placental weight. Phenytoin was not associated with any growth impairment or adverse perinatal outcome.

As our study is based on medical records, for some women data on a number of variables, such as time of treatment, type of epilepsy, and occurrence of seizures, were not available. For a considerable proportion of the offspring, the outcome variables length and head circumference were also missing. An important issue to evaluate is whether the missing variables are the result of selection bias. In that case the results on length and head circumference would be difficult to interpret. However, when comparing weights, which were missing only in 1% of the offspring, between the children with and without length missing, there were no significant differences between the two groups. Also for head circumference findings were similar, suggesting that these variables were not missing for a proportion of offspring on the basis of selection bias, but have occurred randomly.

Controversy remains in the literature whether antiepileptic drugs are associated with growth impairment and/or adverse perinatal outcome. Some studies did show growth impairment associated with antiepileptic drug use during pregnancy[9, 17-21], but others did not[30-32]. In most studies that did show an effect of antiepileptic drugs, associations have been found between antiepileptic drugs and reduced weight or head circumference. Carbamazepine and phenobarbital have also been associated with reduced length[8, 28]. Furthermore, of the four major antiepileptic drugs, phenobarbital has most often been associated with growth impairment[17, 27, 28].

In the present study, antiepileptic drug use during the first trimester of pregnancy was associated with a significantly lower weight, shorter length and smaller head circumference in the offspring compared to non-epileptic controls. The fact that a significant difference could only be shown in this group may in part be explained by the large size of the group and the potentially long exposure to antiepileptic drugs (three trimesters). Head circumference was also significantly smaller in offspring of women using antiepileptic drugs only during second and/or third trimester of pregnancy, suggesting an influence on growth in later stages of pregnancy.

Only offspring of women with valproate use during the first trimester of pregnancy had significantly lower Apgar scores, which has previously been reported by Jäger-Roman et al.[26] They suggested that neonatal distress may have been caused by a high valproate free fraction, which increased threefold during labour and birth. The lower Apgar scores could be associated with a higher percentage of major congenital abnormalities in the offspring exposed to valproate. However, carbamazepines were also associated with elevated risks of major congenital abnormalities, but not with lower Apgar scores. The absence of this effect in carbamazepine exposed offspring suggests that this explanation is less likely.

Lower weight and smaller head circumference were associated with three of the four major antiepileptic drugs; valproate, carbamazepine and phenobarbital. Smaller head circumference was associated with these drugs in monotherapy as well as polytherapy, whereas lower weight and lower placental weight were associated with antiepileptic drugs in polytherapy. A shorter length was only found for carbamazepine monotherapy. Evidence of a dose-response relationship was found only for phenobarbital and head circumference. With respect to possible mechanisms responsible for growth retardation, few studies have been performed. Kaneko et al. suggested that a decrease of the thyroxine level, caused by the antiepileptic drugs, produced the fetal head growth retardation.[24]

Since lower weight and smaller head circumference were also associated with generalized epilepsy and head circumference also with seizure occurrence during first trimester of pregnancy, it remains difficult to attribute the growth impairment to antiepileptic drug use solely. When stratifying for type of epilepsy within the mono- or polytherapy regimens, the results were suggestive of an additive effect of the combination generalized epilepsy and valproate, carbamazepine, or phenobarbital on head circumference, and of generalized epilepsy in combination with valproate on weight. No evidence of interaction was found on Apgar scores.

A reduction in placental weight at birth was found only for children exposed to valproate or phenobarbital. Findings on placental weight were not consistent over the four exposure groups. A reduction in weight was found only in those with maternal use of antiepileptic drugs in first trimester (group I); in all other children exposed to maternal epilepsy placental weight was increased compared to non-epileptic controls (being significant in those exposed to antiepileptic drugs during second and/or third trimester only). The weight of the child at birth was also higher, in pregnancies with maternal epilepsy not exposed to antiepileptic drugs, suggesting that epilepsy by itself may lead to a higher birth- and placental weight, while exposure to antiepileptic drugs (in particular of valproate or phenobarbital) may have opposite effects.

Our study of 4107 pregnancies suggests an effect of antiepileptic drug treatment during pregnancy on development of the fetus, although maternal generalized epilepsy was also associated with lower weight and smaller head circumference. Adverse effects were found for most specific antiepileptic drugs, either in mono- or polytherapy, with the exception of phenytoin. The association between valproate and apgar score suggests that extra attention may be anticipated for children exposed to this antiepileptic drug during delivery and the perinatal period. Antiepileptic drugs as well as the underlying epilepsy appear to play an important role in growth and development of the fetus. The interaction with the type of epilepsy may reflect different types of (genetic) pathways underlying the disease. This may also, in part, explain the inconsistencies between the several studies performed thus far. Different countries have used different prescription policies for antiepileptic drugs, and these policies have also changed within countries in the previous decades. In future studies it will be important to evaluate outcome parameters such as growth in the light of the underlying genes causing the maternal epilepsy.

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Chapter 5.4

Maternal use of carbamazepine and multiple congenital abnormalities and fetal hepatotoxicity in two siblings

5.4 Maternal use of carbamazepine and multiple congenital abnormalities and fetal hepatotoxicity in two siblings

Abstract

This report concerns two siblings with similar patterns of congenital abnormalities and liver cell degeneration. Abnormalities were partly diagnosed prenatally by ultrasound examination, and both pregnancies were terminated at 20 and 19 weeks respectively. The siblings were concordant for severe growth retardation, shortening of extremities, enlarged brain ventricles, increased heart/thorax ratio, agenesis or hypoplasia of one of the umbilical arteries, irregular glomerulogenesis with focal calcifications, and liver cell degeneration. The male sibling also had severe hypospadias. In both pregnancies, the mother had used chronically carbamazepine because of idiopathic primary generalised epilepsy. A pregnancy without exposure to carbamazepine, resulted in the birth of a healthy girl. This unique combination of an extremely rare fetal abnormality pattern and fetal hepatotoxic abnormalities with maternal carbamazepine use suggests that these abnormalities are due to an interaction between a rare genetic predisposition and carbamazepine exposure, and that carbamazepine-induced teratogenesis and hepatotoxicity may have a common mechanism.

Introduction

Antiepileptic drug use during pregnancy is associated with an increased risk of congenital abnormalities in the offspring.[1-6] Abnormalities reported in association with maternal carbamazepine use are open neural tube defects,[7-9] congenital heart malformation,[10, 11] hypospadias,[12] and facial clefts.[13] The role of genetic predisposition in carbamazepine-induced teratogenesis has not been established so far,[14, 15] but clinical and experimental studies suggest the significance of gene-environment interaction in antiepileptic drug-induced teratogenesis in general.[16-19]

Also severe idiosyncratic hepatotoxicity with carbamazepine use has been reported in a small number of adult patients.[20, 21] In vitro studies of lymphocytes from some of these patients indicated a role of genetic predisposition for this idiosyncratic side effect.[22, 23] However, experimental studies have not been successful so far in further delineation of the putative role of genetic factors. It is also unknown what the mechanisms of action are, and whether they are the same for teratogenesis and hepatotoxicity.

This report describes two siblings with a similar, previously unreported pattern of multiple congenital abnormalities as well as fetal liver cell degeneration after maternal

use of carbamazepine during both pregnancies, suggesting a genetic predisposition and common mechanism to at least some of the carbamazepine-induced adverse foetal effects.

Clinical report

This medical history came to our knowledge in two different ways, through a retrospective follow-up study of pregnancy outcome in maternal epilepsy in the Netherlands, and through a referral for genetic counselling to the Department of Clinical Genetics at the Academic Hospital Rotterdam, and summarises data from both sources.

The 25 year old woman, with primary generalized epilepsy since the age of seven years, was referred to the outpatient clinic for prenatal diagnosis of the University Hospital Rotterdam/Dijkzigt, because of the well known increased risk of a neural tube defect due to carbamazepine use (twice daily 100 mg) in pregnancy. At intake, amenorrhoea was 12 weeks. At 16 weeks, amniocentesis was performed. Cytogenetic analysis of cultured amniocytes showed a normal male karyogram (46,XY). The alpha-fetoprotein level in the amniotic fluid was 23,5 μg/ml (normal upper limit for this stage of pregnancy in our laboratory: 41 μg/ml). At 19 4/7 weeks, structural fetal ultrasound screening was performed, which revealed severe growth retardation, predominantly of the extremities, enlargement of all brain ventricles, and an increased heart/thorax ratio. After full information, the parents opted for termination of pregnancy which was performed with Nalador^{R} infusion. Autopsy showed a male foetus of 47 gram, with a crown rump length (CRL) of nine cm, length of 14 cm and a head circumference of 11 cm, equivalent to a fetal age of 15 weeks (extreme growth retardation). The foetus showed bilateral cheilo-gnato-palatoschisis, severe hypospadias, agenesis of the right umbilical artery, severely malformed skull, with skull defect and without brain *in situ*, irregular glomerulogenesis with focal calcifications, and a liver with acute hemi-lateral hepatic cell degeneration. There was an extensive congestion of parenchymatous organs and multiple bleedings due to asphyxia. Postnatal chromosome analysis of foetal tissue was not possible. TORCH and hepatitis serology of the mother did not provide evidence for a foetal infection. During pregnancy, there had been no epileptic seizures, and no other intercurrent diseases or complications. The mother had not used alcoholic beverages or tobacco, nor did she use any other social drug or medication. The family history was negative for congenital abnormalities, liver disease, or epilepsy. There was no parental consanguinity.

During her second pregnancy at the age of 26 she did not use carbamazepine. Medication was stopped one month before her last menstruation. Amniocentesis at 17 weeks with cytogenetic analysis of amniocytes showed a normal female karyogram (46,XX) and normal alpha-fetoprotein level. Ultrasound screening at 19 weeks showed no foetal anomalies. At 37 weeks of pregnancy a healthy girl was born with a weight of 2600 gram, a length of 49 cm, a head circumference of 34 cm, and Apgar scores of 8 and 9 after one and five minutes respectively.

Before her third pregnancy at the age of 28, carbamazepine medication was again stopped one month before the last menstruation. This pregnancy though, ended at 15 weeks in a miscarriage. Pathological examination of the aborted tissue showed no abnormalities.

From before and throughout her fourth pregnancy, the mother (age 31) used daily 200 mg of carbamazepine and 5 mg of folic acid. The foetal karyogram was normal (46,XX) as was the alpha-fetoprotein level in amniotic fluid. Structural ultrasound screening at 18 weeks revealed enlargement of all brain ventricles, severely shortened extremities, increased heart/ thorax ratio and intra-abdominal calcifications. The parents again opted for termination of pregnancy, which was performed at 19 weeks. Autopsy showed a female foetus of 54 gram, CRL of 10,5 cm, and length of 14,1 cm (extreme growth retardation). The foetus showed an internal hydrocephalus, and other cerebral abnormalities characterised by migration disturbances. Further microscopic examination revealed liver cell degeneration, an irregular glomerulogenesis with calcifications and thymus atrophy. Pathologic examination of the placenta showed hypoplasia of one umbilical artery. During pregnancy, drug analysis of amniotic fluid and maternal serum had not been performed. Additional analysis of stored maternal serum and amniotic fluid samples demonstrated the presence of carbamazepine, the 10,11-epoxide and 10,11-diol metabolites of carbamazepine and of caffeine.

Discussion

We have presented a G4/P3/A1 mother with epilepsy who had given birth to two children with a similar pattern of multiple congenital abnormalities as well as foetal liver cell degeneration while on carbamazepine during pregnancy. She also had delivered a healthy child while using no antiepileptic drugs during pregnancy.

Liver cell degeneration as a result of carbamazepine use is not as common as with valproate.[24-27] Carbamazepine-induced liver cell degeneration has been described in a number of adults,[20, 21] with liver cell regeneration after discontinuation of the drug, but not in neonates. The pattern of congenital abnormalities in the two affected foetuses

is almost identical, and consists partly of abnormalities that have been reported previously in association with carbamazepine use during pregnancy. Carbamazepine use during pregnancy is mainly associated with neural tube defects, including spina bifida aperta, hydrocephalus, and rarely encephalocele, hypospadias, and possibly also with a number of other defects like congenital heart abnormalities and facial clefts.[7-9, 12, 13] In addition, both foetuses also showed severe growth retardation, with shortened extremities.

An extensive literature search and consultation of the London Dysmorphology Data Base (LDDB), London Neurology Data Base (LNDB) and POSSUM (Pictures of Standard Syndromes and Undiagnosed Malformations) did not result in the diagnosis of a previously reported or well known syndrome. Cytogenetic analysis of cultured amniocytes excluded a familial chromosome translocation as a cause.

The pattern of abnormalities in these two affected siblings is rare, as is the case for prenatal exposure to carbamazepine which is estimated at about 1 per 1,000 pregnancies. The daily dose used by the mother was rather low. This suggests that the foetal abnormalities were due to an interaction between a genetic predisposition and carbamazepine exposure, although a pure genetic cause can not be excluded. The co-occurrence of congenital abnormalities and foetal liver cell degeneration also indicates that carbamazepine-induced teratogenesis and hepatotoxicity may have a common pathogenetic mechanism, in contrast to valproate-induced idiosyncratic side effects.

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Chapter 6

General discussion

6. General discussion

6.1 Introduction

In this thesis, the studies on associations between antiepileptic drugs, maternal epilepsy and fetal outcome have been described. Findings of the European collaborative reanalysis of prospective follow-up studies showed an increased risk of major congenital abnormalities in children exposed to antiepileptic drugs during pregnancy. In particular, a significant increase in risk was found for children exposed to valproate (dose-response) and carbamazepine monotherapy, the combination of phenobarbital with ethosuximide and the combination of phenytoin, phenobarbital, carbamazepine and valproate. The methodological issues relevant for a reanalysis have been discussed elsewhere (see Chapter 4).[1,2] In this final chapter the main findings of the retrospective population-based follow-up study conducted in The Netherlands will be summarized and some methodological issues of this study will be discussed. The clinical implications of the results of the study will be addressed and finally some suggestions for further research will be made.

6.2 Main findings

The main results on the association between the four maternal exposure groups and major congenital abnormalities in the offspring, described in Chapter 5.1, are summarized in table 6.2.1. We found an increased risk of major congenital abnormalities associated with antiepileptic drug use during first trimester of pregnancy, which is the teratogenic period for organogenesis. Furthermore, we found evidence for an increased relative risk of major congenital abnormalities in the offspring of women with only second and/or third trimester exposure to antiepileptic drugs, in particularly associated with partial epilepsy or the occurrence of seizures during the first trimester of pregnancy. These women were not treated in the teratogenic period of embryogenesis, making it difficult to ascribe a teratogenic effect to the antiepileptic drug. However, we can not exclude that some of these women had restarted medication by themselves already during first trimester in which case the increased risk of major congenital abnormalities might be antiepileptic drug-induced. On the other hand, the partial epilepsy in the mother and the major congenital abnormalities in the child may be due to a common genetic predisposition resulting in an increased risk of abnormalities, whereas seizure occurrence during the first trimester of pregnancy also may be a causative teratogenic determinant in the development of major congenital abnormalities.

Table 6.2.1 *Relative risk (95% confidence interval) of major congenital abnormalities in the offspring of women with epilepsy, adjusted for age and parity.*

Exposure group	N[a] (%)	RR (95% CI)	Comments
Non-epileptic controls	29/2000 (1.5%)	1.0 reference	
AED[b] in first trimester	52/1411 (3.7%)	2.6 (1.6-4.1)	
AED only in second and/or third trimester	4/115 (3.5%)	2.6 (0.9-7.7)	Association with partial epilepsy or seizures during first trimester
AED unknown trimester	2/79 (2.5%)	1.6 (0.4-6.8)	
Epilepsy without AED	7/421 (1.7%)	1.2 (0.5-2.8)	Association with generalized epilepsy

[a] Numbers are abnormalities/total exposed pregnancies
[b] AED = antiepileptic drugs

The relation between antiepileptic drug regimen and major congenital abnormalities was studied in Chapter 5.2. The main results are presented in table 6.2.2. We found a significantly increased risk of major congenital abnormalities for carbamazepine and valproate monotherapy, with evidence for a significant dose-response relationship for valproate. The findings for valproate are in line with the reanalysis of the European prospective studies. In the Dutch retrospective study we further found evidence for a role of caffeine in teratogenesis. The risk of major congenital abnormalities was non-significantly increased for phenobarbital monotherapy, when caffeine co-medication was excluded. However, when caffeine was included, a significant increase in risk was found. Phenytoin monotherapy was not associated with an increased risk of major congenital abnormalities. Regarding polytherapy regimens, increased risks were found for several specific antiepileptic drug combinations. Clonazepam in combination with other antiepileptic drugs showed a significantly increased relative risk.

Furthermore, there was a significantly increased relative risk for the combination of carbamazepine and valproate and the combination of phenobarbital and caffeine with other antiepileptic drugs. Valproate +/- other antiepileptic drugs and valproate + carbamazepine were significantly associated with spina bifida and valproate +/- other antiepileptic drugs with hypospadias.

Finally, we studied the relation between maternal epilepsy or antiepileptic drugs and fetal growth and perinatal outcome. The results are summarized in table 6.2.3.

Table 6.2.2 *Relative risk (95% confidence interval) of major congenital abnormalities in offspring associated with exposure to antiepileptic drugs in monotherapy and polytherapy and co-medication.*

Exposure	Therapy	N[a] (%)	RR (95% CI)	Comments
Phenobarbital	mono	5/172 (3%)	2.0 (0.8-5.3)	Dose-response relationship
	poly	11/276 (4%)	2.8 (1.4-5.7)	Interaction with caffeine
Phenytoin	mono	1/151 (1%)	0.5 (0.1-3.4)	
	poly	6/209 (3%)	2.0 (0.8-4.9)	
Carbamazepine	mono	14/376 (4%)	2.6 (1.4-5.0)	
	poly	12/222 (5%)	3.5 (1.7-7.2)	
Valproate	mono	9/158 (6%)	4.1 (1.9-8.8)	Dose-response relationship
	poly	8/136 (5%)	3.7 (1.6-8.6)	Association with spina bifida and hypospadias
Benzodiazepines	mono	0/25 (0%)	-	
	poly	6/106 (6%)	4.1 (1.7-10.1)	Clonazepam, diazepam, clobazam
Caffeine	mono	-	-	
	poly	5/75 (7%)	4.9 (1.8-12.9)	Interaction with phenobarbital

[a] Numbers are abnormalities/total exposed pregnancies

We found that offspring of women with epilepsy using antiepileptic drugs during pregnancy had significantly lower weight, shorter length and smaller head circumference compared to non-epileptic controls. Lower weight and smaller head circumference were also associated with generalized epilepsy and seizure occurrence during first trimester of pregnancy (only head circumference). Offspring of women using valproate monotherapy during the first trimester of pregnancy had significantly lower Apgar scores than non-epileptic controls and valproate polytherapy was associated with a significantly decreased weight and placental weight.

Carbamazepine monotherapy was associated with a significantly shorter length and smaller head circumference, while carbamazepine polytherapy was associated with a significantly lower weight and smaller head circumference. Phenobarbital monotherapy was associated with a significantly smaller head circumference, and phenobarbital polytherapy was associated with a significantly lower weight, smaller head

Table 6.2.3 *Association between maternal epilepsy and antiepileptic drugs and growth parameters and Apgar score at 5 minutes. Unless stated otherwise, the association indicates a decreased measure for the offspring of women with epilepsy compared to non-epileptic controls.*

Exposure		Weight	Length	Head circumference	Apgar score at 5 minutes	Comments
AED in first trimester		+	++	++	-	
Valproate	mono	-	-	-	+	
	poly	+[1]	-	++[1]	±	[1] Interaction with generalized epilepsy
Carbamazepine	mono	-	++	++[1]	-	[1] Interaction with generalized epilepsy
	poly	+[2]	-	++[1]	+	[1] Interaction with generalized epilepsy, [2] Interaction with other types of epilepsy
Phenobarbital	mono	-	-	++[1,3]	-	[1] Interaction with generalized epilepsy, [3] dose-response relation
	poly	++	-	++	±	
Phenytoin	mono	-	-	-	-	
	poly	-	-	-	+	
AED only in second and/or third trimester		-	-	+	-	
AED unknown trimester		-	-	±	-	
Epilepsy without AED		+[4]	-	-	±	[4] higher weight with maternal epilepsy
Generalized epilepsy		++	+	++	+	
Partial epilepsy		-	-	+	-	
Unknown epilepsy		++	-	++	-	
Seizures during first trimester		-	-	+	-	

(++) = strong significant association, (+) = significant association, (±) = suggestive for an association, (-) = no association

circumference, and lower placental weight. Phenytoin was not associated with any growth impairment or adverse perinatal outcome.

6.3 Methodological issues

Before the clinical relevance of the findings can be evaluated, methodological issues including precision and validity in the retrospective population-based follow-up study conducted in The Netherlands have to be addressed. A major advantage of a retrospective population-based follow-up study is, that in a relatively short time a large number of pregnancies can be collected from a homogeneous population. This is particularly important if the exposure variable, such as maternal epilepsy (3-5 in every 1000 pregnancies) is relatively uncommon, and if large numbers of pregnancies are needed to evaluate differences in prevalence of rare major congenital abnormalities with regard to specific antiepileptic drug regimens. However, there are potential pitfalls of this design in term of validity, which will be discussed below.

Precision

The size of the group under investigation is important with regard to the precision or the reproducibility of the study. The larger the number of subjects, the smaller the variance of the risk estimates.[3, 4] In particular for clinical applications, precise estimates of risks are required for the different aspects of maternal epilepsy relevant for teratogenesis. Despite the large number of pregnancies studied over a period of 20 years in the study, the numbers for some antiepileptic drug regimen still remained too small to evaluate an association with major congenital abnormalities. This indicates that even larger numbers of pregnancies, targeted toward specific antiepileptic drug regimens, monotherapy as well as polytherapy, are needed to quantify the relation between these specific antiepileptic drugs and major congenital abnormalities.

Validity

Another important issue in epidemiologic research is the validity of a study, which refers to the issue whether the observed results represent a true estimation of risk of adverse pregnancy outcome. In any observational study it is of great importance to address alternative explanations for an observed association such as selection bias, information bias or confounding.[3, 4]

Selection bias

Selection bias may have occurred in our studies if the choice of exposed and non-exposed individuals was related to the development of the outcome of interest. Selection bias may particularly be a problem in retrospective follow-up studies, where both exposure and outcome have already occurred at the time of selection of individuals. In this study the population comprised of hospital deliveries. Since epilepsy is a medical indication for hospital delivery in The Netherlands, all children with maternal epilepsy are expected to be ascertained through hospital deliveries. Pregnancies exposed to antiepileptic drugs, but terminated after prenatal diagnosis, were also included. The non-epileptic control pregnancies were selected from the same hospital as the exposed. In The Netherlands, there are two options for delivery, at home or at the hospital. The latter deliveries may be enriched with pregnancies with a medical indication for hospital delivery. It is impossible to exclude that the non-epileptic controls were enriched for other risk factors than those associated with maternal epilepsy, thus contributing to the development of major congenital abnormalities, growth impairment or adverse perinatal outcome. It is important to realise in light of clinical implications, that this type of bias would imply a dilution of the true effects of antiepileptic drugs on the risk of major congenital abnormalities, growth impairment or adverse perinatal outcome, and the findings of our studies may therefore have been underestimated. The prevalence of major congenital abnormalities in the non-epileptic controls was 1.5%, which is similar to the expected frequency in The Netherlands (1-2%),[5] suggesting that the control population has not been enriched with high risk factor for the development of major congenital abnormalities.

Finally, to exclude the possibility, that increased risk of major congenital abnormalities for pregnancies exposed to maternal epilepsy were due to other risk factors, exposed and non-epileptic controls were matched for age and parity of the mother, sex, place and year of birth of the child. Groups were also compared for other potentially teratogenic maternal conditions, including diabetes mellitus and other disorders related to major congenital abnormalities.

Information bias

Information bias will occur when information on exposure or outcome is systematically obtained in a different way for the two study groups to be compared. In our study, the assessment of congenital abnormalities in the offspring, might have differed for the maternal epilepsy group and for the non-epileptic controls. There has been an increasing interest for teratogenic effects of drugs, in particular antiepileptic

drugs. This may have led to an increased awareness of major congenital abnormalities in offspring of women with epilepsy using antiepileptic drugs. Consequently, when a child is born to a mother with epilepsy, the child may have been examined more thoroughly for congenital abnormalities and both the detection and registration of the abnormality may have differed from that in non-epileptic control pregnancies. We tried to overcome this problem in our study by focusing on (obviously) visible defects such as spina bifida aperta, hypospadias, abdominal defects, facial clefts, defects of the extremities and severe congenital heart abnormalities, thus making the occurrence of information bias less likely. On the other hand, our study has been conservative, since associations with major congenital abnormalities presenting in later phases of life, such as congenital heart defects, may have been missed.

An important source of information bias in the retrospective study may result from missing data. Because our study is based on medical records, data on a number of variables, such as time of treatment and dose of antiepileptic drugs, type of epilepsy, occurrence of seizures, and family history were not available for a substantial number of women. For a considerable proportion of the offspring the outcome variables length and head circumference were missing. An important issue to evaluate is whether the missing variables have resulted in information bias. We have addressed this issue specifically in Chapter 5.3. There were no significant differences in weight between the offspring, for whom variables such as length and head circumference were missing and the offspring, for whom these variable were not missing. There were also no significant differences between the exposed and the non-epileptic controls with regard to missing variables, suggesting that these missings have occurred randomly.

Confounding bias

Whereas selection bias and information bias are introduced by the study design, confounding bias is a function of the complex interrelationship between various exposures and outcome. In our study the most important type of confounding bias may be confounding by indication. Here confounding by indication implies that certain types of epilepsy, with increased risks of abnormalities by itself, may be treated specifically with certain antiepileptic drugs. Consequently, a spurious association between the antiepileptic drugs and major congenital abnormalities may be found, that in fact can be ascribed fully to the type of epilepsy. Although it is difficult to exclude confounding by indication in an observational study, we found no clear evidence for an association between any type of epilepsy and major congenital abnormalities in offspring of women using antiepileptic drugs during first trimester of pregnancy. This

suggests that type of epilepsy itself is not associated with an increased risk of major congenital abnormalities and makes confounding by indication less likely. We did however find evidence for an association between major congenital abnormalities and antiepileptic drug exposure in second and/or third trimester only, for offspring of women with partial epilepsy or seizures during first trimester, and not for offspring of women with other types of epilepsy. These children were not exposed to antiepileptic drugs in the period of embryogenesis, suggesting that the partial epilepsy in the mother and the major congenital abnormalities in the child may be due to a common genetic predisposition or the result of transplacental noxious influences.

Other important risk factors with regard to confounding are age and parity of the mother, and sex, year and place of birth of the child. Year and place of birth could be important risk factors if associated with environmental factors, e.g. pollution and drug exposure. In order to prevent confounding, the non-epileptic controls have been matched to the exposed pregnancies for these variables.

Finally, bias may be related to the fact that multiple pregnancies of a woman were included. If a genetic predisposition might play a role in teratogenesis, multiple pregnancies form the same mother could skew the results. We therefore performed an analysis in which only the first pregnancy of a woman entered in the study was used, and we performed an analysis stratifying by parity. The risk of major congenital abnormalities did not change materially.

6.4 Clinical implications

In line with clinical practice in which antiepileptic drugs are prescribed, clinical implications will be discussed first by antiepileptic drugs. For reliable recommendations concerning antiepileptic drug use in pregnancy, it is important to base these recommendations on results from regimens with numbers large enough to report reasonably stable risk estimates. Therefore we will focus on antiepileptic drug regimens frequently prescribed in this study population (n>50) and antiepileptic drug regimens which have previously been reported to be associated with major congenital abnormalities.

Antiepileptic drugs associated with outcome

Phenobarbital

For phenobarbital monotherapy we found a non-significantly increased risk of major congenital abnormalities, which was dose-dependent, and an additive effect of caffeine co-medication on major congenital abnormalities. Furthermore, phenobarbital

monotherapy was associated with a significantly smaller head circumference, for which we also found evidence for interaction between phenobarbital monotherapy and generalized epilepsy.

For phenobarbital polytherapy we found a significantly increased risk of major congenital abnormalities, and a suggestion for interaction of caffeine co-medication. Further, phenobarbital polytherapy was associated with a significantly lower weight and small head circumference.

Phenytoin

Phenytoin polytherapy was associated with lower Apgar scores at 5 minutes.

Carbamazepine

For carbamazepine monotherapy we found a significantly increased risk of major congenital abnormalities and significantly shorter length and smaller head circumference. Carbamazepine polytherapy was also associated with a significantly increased risk of major congenital abnormalities and with a significantly lower weight and head circumference. With regard to head circumference, mono- as well as polytherapy showed interaction with generalized epilepsy.

Valproate

For valproate monotherapy we found a significantly increased risk of major congenital abnormalities, which was dose-dependent, and significantly lower Apgar scores at 5 minutes.

Valproate polytherapy was also associated with an increased risk of major congenital abnormalities, and with a significantly lower weight and smaller head circumference. The results showed interaction between valproate polytherapy and generalized epilepsy with regard to weight and head circumference. Furthermore, valproate polytherapy showed a strong association with spina bifida, especially in case of valproate with carbamazepine, and also an association with hypospadias.

Benzodiazepines

Benzodiazepines in polytherapy showed a significantly increased risk of major congenital abnormalities, in particular clonazepam, diazepam and clobazam, and especially in combination with valproate or carbamazepine.

Co-medication

Caffeine has often been used as co-medication to counterbalance the sedative effect of phenobarbital. We found a significantly increased risk of major congenital abnormalities associated with caffeine polytherapy in combination with phenobarbital. The relative risk of caffeine with phenobarbital with other antiepileptic drugs was 5.1

(95% confidence interval: 1.5-17.4). Although this finding remains to be confirmed, it underscores the potential relevance of apparently harmless additives to drugs with regard to teratogenesis.

Maternal factors associated with outcome

Seizure occurrence during first trimester of pregnancy was significantly associated with major congenital abnormalities in the offspring exposed to antiepileptic drugs in second and/or third trimester only and with a smaller head circumference in offspring exposed to antiepileptic drugs during first trimester of pregnancy. Finally, we found an association between major congenital abnormalities and antiepileptic drug exposure only in second and/or third trimester for offspring of women with partial epilepsy. Regarding fetal growth and perinatal outcome, we found an association between generalized epilepsy and impaired growth and reduced Apgar scores.

Implications

Several of the findings above concerning pregnancy outcome have been reported before. Differences in risk of the four major antiepileptic drugs concerning major congenital abnormalities have not been established yet.[6]

Phenytoin and phenobarbital have been associated with congenital heart defects and facial clefts,[7, 8] and are considered to be equally teratogenic as the other antiepileptic drugs. Valproate has been associated with high risks of spina bifida and hypospadias.[9-12], and although carbamazepine also has been associated with neural tube defects,[13, 14] many neurologists consider carbamazepine monotherapy a safe alternative in pregnancy.[15] Concerning fetal growth and perinatal outcome findings of previous studies have been inconsistent, but an association with growth retardation has been reported for carbamazepine and phenobarbital use during pregnancy,[16-19] and an association with adverse perinatal outcome for valproate.[20]

In our study we found a significantly increased risk of major congenital abnormalities associated with carbamazepine mono- and polytherapy, and in contrast with previous studies we found a very low risk of major congenital abnormalities for offspring exposed to phenytoin monotherapy compared to non-epileptic controls. However, the low risk found for this drug may be the result of an underascertainment of congenital heart defects. Furthermore, the fetal hydantoin syndrome (consisting of pre- and postnatal growth retardation, microcephaly and developmental delay, combined with dysmorphic features such as craniofacial abnormalities and nail and distal phalangeal hypoplasia)[21] is not incorporated within the definition of a major

congenital abnormality and has not been included as a study outcome. Our current cohort comprises a relatively large proportion of phenytoin monotherapy, whereas previously reported associations with congenital abnormalities were usually found for phenytoin polytherapy. Thus, the results on phenytoin should be interpreted carefully, although phenytoin exposure during pregnancy was not found to be associated with prenatal growth retardation. On the other hand, phenytoin monotherapy might be less teratogenic than thought before, and should perhaps not be regarded as obsolete when seizure control is optimal with this drug. All other antiepileptic drugs, in mono- as well as in polytherapy, showed an increased risk of major congenital abnormalities compared to the non-epileptic controls. In general, risks of major congenital abnormalities were higher for polytherapy, except for valproate. Furthermore, we found a significantly increased risk associated with caffeine as co-medication, especially in combination with phenobarbital.

Since all the antiepileptic drugs under investigation pose some degree of threat to pregnancy outcome, with regard to major congenital abnormalities as well as growth and perinatal outcome, none of the drugs can be regarded as safe. Of the polytherapy regimens, in particular the combination of carbamazepine and valproate, benzodiazepines (especially clonazepam) in polytherapy, and phenobarbital with caffeine, were associated with high risks of major congenital abnormalities. Caffeine is not prescribed as co-medication any more in The Netherlands, but it may in other countries. The high risk found for caffeine in combination with phenobarbital, implies that caffeine as a chemical drug should not be used during first trimester of pregnancy. The role of caffeine intake as medication may differ from caffeine ingested through social drinks and depend on differences in bioavailability and magnitude of exposure during the first half of pregnancy, a period known for high frequency of coffee aversion.

An important finding of our study is that, in contrast to other studies, our findings show that carbamazepine monotherapy is not a safe drug, since it was associated with major congenital abnormalities as well as impairment of several growth parameters.

In addition to major congenital abnormalities, in particular neural tube defects and hypospadias, valproate monotherapy was also associated with an increased risk of an Apgar score ≤ 6 at five minutes. This finding urges for increased perinatal care, in order to prevent perinatal distress.

In offspring exposed to antiepileptic drugs **only** during second and/or third trimester of pregnancy, seizure occurrence during first trimester was associated with an increased risk of major congenital abnormalities, whereas in children exposed to

antiepileptic drugs during first trimester, seizure occurrence in first trimester was also associated with smaller head circumference. Thus it is important to prevent seizure during pregnancy, especially in the first trimester. In clinical practice the risk of antiepileptic drug exposure should be weighed against the risk of seizures, depending on the type of abnormalities that the antiepileptic drug is associated with.

For valproate monotherapy and to a smaller extent for phenobarbital, we found a dose-response relationship. If withdrawal of these drugs is not possible in order to maintain sufficient seizure control, these drugs should be prescribed in the lowest possible dose. Experimental research indicates that the teratogenic effect of valproate is also considered to result from high peak serum levels and therefore it is preferable to spread the total daily dose in at least two or three administrations per day or prescribe slow release preparations.[22]

Primary and secondary prevention has been discussed in Chapter 2. Primary prevention concerns folic acid supplementation.[23] In our study based on medical records, information on folic acid use was not available for a considerable proportion of pregnancies. However, in general, women with epilepsy are advised to use periconceptional folic acid supplementation of 0.4-0.5 mg/day.[24] Secondary prevention concerns prenatal screening for major congenital abnormalities. The results presented in this thesis justify the performance of amniocentesis, in case of valproate or carbamazepine use.[11, 25] AFP analysis of amniotic fluid and ultrasonography is the method of choice, since there exists doubt about the reliability of AFP analysis of maternal serum in valproate-induced open neural tube defects.[26]

6.5 Further research

Despite the large number of pregnancies studied over a period of 20 years, the numbers for some antiepileptic drug regimen in this study still remain too small to evaluate an association with major congenital abnormalities and provide reliable risk estimates. Large multi-centre prospective follow-up studies are needed in order to study sufficient numbers of pregnancies. Furthermore, studies on interaction with type of epilepsy are needed, and accurate information on type and etiology of epilepsy should be retrieved for all pregnancies in a study. Clinical dysmorphological evaluation should not only be performed in the prenatally exposed offspring, but for comparison also of both parents, and include anthropometric measures such as height and head circumference. Studies on the genetic background of epilepsy might resolve many of the questions that still remain with regard to the possibility of a common etiology of major congenital abnormalities and epilepsy. Family studies and eventually population-

based studies may indicate whether genetic factors predisposing for specific types of epilepsy are associated with a higher prevalence of major congenital abnormalities within families and whether major congenital abnormalities within families are associated with the same gene. Currently, molecular genetic analysis of monogenic epilepsies is making rapid progress. Several idiopathic generalized and partial epilepsy syndromes with autosomal dominant mode of inheritance and variable expression have been mapped, and a number of genes predisposing to these syndromes have been identified. In the forthcoming years, this line of research will probably be extended with success to the more common idiopathic epilepsies with more variable expression and irregular inheritance. Progress has also been made in unravelling the genetics of major congenital abnormalities, including neural tube defects. Whether genetic or predisposing factors for such congenital abnormalities play a role independently from maternal epilepsy by interacting with the teratogenic activity of antiepileptic drugs is another challenge for the near future. If the molecular genetic basis of a significant proportion of maternal epilepsies and major congenital abnormalities is resolved, molecular genetic analysis of DNA of prenatally exposed offspring, with and without congenital abnormalities, will help to determine the contribution of such epilepsy genes in the development of abnormalities in the fetus.

Another important issue for further studies is the potential teratogenic effect of co-medication such as caffeine. Caffeine has not been associated with major congenital abnormalities previously,[29-33] but most of the studies concerned predominantly caffeine ingestion with coffee and other social drinks, and not as a pharmaceutical preparation. Caffeine intake through other sources than coffee, tea, cola and aspirin may reach high dosages in many pregnant women, and it remains important to evaluate a potential teratogenic effect of this drug. The question remains whether caffeine intake from other sources, such as coffee, tea, cola, and aspirins, should be reduced. The dosages of caffeine in our study varied between 75 and 180 mg daily. A cup of coffee on average contains 100 mg of caffeine.[27] Drinking 3 or 4 cups daily would contribute to 300-400 mg of caffeine, which is much higher than the dosages that caused congenital abnormalities in this study. However, the actual total daily ingestion of caffeine from dietary sources is also influenced by bioavailability and pregnancy induced coffee aversion. In light of the effects observed in this thesis, other dietary factors may also interact.

Our retrospective study provides information from the past 20 years. In the past ten years, over ten new antiepileptic drugs have been developed and these drugs are now being released for prescription in many countries. Some of these drugs have been

proven to be teratogenic in animal studies.[28] Others were not teratogenic in animal studies, but in view of interspecies differences in susceptibility, these drugs should also be followed closely in order to identify any adverse effect in humans as soon as possible. Our study shows that caution is warranted with the introduction of new drugs in humans, and that immediate monitoring of the effects of these drugs with regard to congenital abnormalities is necessary. Initiatives have already been taken by a number of European countries to set up a multi-centre prospective follow-up study for such monitoring, and clinicians responsible for the well-being of patients will have to collaborate with pharmaceutical companies, in order to detect adverse effects as early as possible.

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Chapter 7

Summary
Samenvatting

7.1 Summary

The aim of the studies presented in this thesis was to quantify the risk of adverse pregnancy outcome associated with maternal epilepsy and antiepileptic drugs, in particular with regard to abnormalities, fetal growth and perinatal outcome associated with specific antiepileptic drug regimens, the occurrence of a dose-response relationship, and the role of type of epilepsy and seizure occurrence during pregnancy (***Chapter 1***).

Chapter 2 presents an overview of studies performed earlier, risks and patterns of abnormalities associated with several antiepileptic drugs, dose-response relationships and deals with primary and secondary prevention.

The rationale of the thesis was to examine the teratogenic effects of antiepileptic drugs and maternal epilepsy in population-based cohorts with large numbers of exposed pregnancies. We have performed two population-based studies, and in ***Chapter 3*** an outline of the design of the two studies is given. The first study is a reanalysis of five prospective studies on the role antiepileptic drugs in pregnancy outcome, conducted in Europe between 1971 and 1990. The second study involves a retrospective population-based follow-up study in the southwestern area of the Netherlands.

Chapter 4 describes the results of a reanalysis of five prospective studies on the of role antiepileptic drugs on pregnancy outcome, conducted in Europe between 1971 and 1990. For this study data from five prospective studies, with a total of 1379 children, were pooled. There was an increased risk of major congenital abnormalities in children exposed to antiepileptic drugs during pregnancy (relative risk (RR) 2.3, 95% confidence interval (CI): 1.2 - 4.7). A significant increase in risk was found for children exposed intra-uterinely to valproate (RR 4.9, CI: 1.6 - 15.0) or carbamazepine (RR 4.9, CI: 1.3 - 18.0) in monotherapy. When comparing different antiepileptic drug regimens during all 1221 pregnancies, risks of major congenital abnormalities were significantly increased for the combination of phenobarbital and ethosuximide (RR 9.8, CI: 1.4 - 67.3) and the combination of phenytoin, phenobarbital, carbamazepine and valproate (RR 11.0, CI: 2.1 - 57.6). Offspring of mothers using more than 1000 mg valproate/day were at a significantly increased risk of major congenital abnormalities (including predominantly neural tube defects) compared to offspring exposed to 600 mg valproate/day or less (RR 6.8, CI: 1.4 - 32.7). No difference in risk of major congenital abnormalities was found between the offspring exposed to 601-1000 mg/day and 600 mg/day or less. This reanalysis showed that valproate is consistently associated

with an increased risk of major congenital abnormalities in the offspring. Furthermore, although the data of five studies were pooled, the number of women exposed remained small for a considerable number of drug combinations, leading to instable risk estimates. It has underlined the risks of the antiepileptic drugs, but has also demonstrated the need for further research and for studies including even larger number of pregnancies, as presented in the following chapters.

Chapter 5 describes the results of the retrospective population-based follow-up study in the southwestern area of the Netherlands.
In ***Chapter 5.1*** the relation between exposure groups (I_IV) (*see Chapter 3*) and major congenital abnormalities were studied. Offspring exposed to antiepileptic drugs in the first trimester of pregnancy had an increased risk of major congenital abnormalities (RR = 2.6, CI: 1.6-4.1). Children prenatally exposed to antiepileptic drugs, but **not** during the first trimester of pregnancy, also showed an increased risk of major congenital abnormalities. In this group major congenital abnormalities were found to be associated with maternal partial epilepsy (RR 5.1, CI: 1.5-17.4) and seizures during first trimester (RR 7.2, CI: 1.6-32.2). Children of mothers with epilepsy not exposed to antiepileptic drugs throughout pregnancy showed no increased risk of major congenital abnormalities compared to the non-epileptic control population. The study shows a teratogenic effect of antiepileptic drug treatment during pregnancy. Furthermore, it strongly suggests that a subpopulation of women with only second and/or third trimester exposure to antiepileptic drugs are at a relatively high risk of having malformed offspring, in particularly associated with partial epilepsy or the occurrence of seizures during pregnancy. The results support a role of type of epilepsy and the risks of seizures during pregnancy.

In ***Chapter 5.2*** the association between specific antiepileptic drug regimens and major congenital abnormalities was studied. We found a significantly increased risk of major congenital abnormalities for carbamazepine (RR 2.6, CI: 1.4-5.0) and valproate monotherapy (RR 4.1, CI: 1.9-8.8), with a significant dose-response relationship for valproate. Offspring of mothers using ≥ 1000 mg valproate/day were at a significantly increased risk of major congenital abnormalities compared to offspring exposed < 600 mg valproate/day (RR 3.9, CI: 1.4-11.1). The risk of major congenital abnormalities was non-significantly increased for phenobarbital monotherapy (RR 2.0, CI: 0.8-5.3), when caffeine co-medication was excluded. However, when caffeine was included, a significant increase in risk was found (RR 2.6, CI: 1.1-6.0). Phenytoin monotherapy was not associated with an increased risk of major congenital abnormalities (RR 0.5,

CI: 0.1-3.4). Regarding polytherapy regimens, increased risks were found for several antiepileptic drug combinations. Benzodiazepines in combination with other antiepileptic drugs showed a significantly increased relative risk (RR 4.1, CI: 1.7-10.1). Furthermore, there was a significantly increased relative risk for the combination of carbamazepine and valproate (RR 5.0, CI: 1.7-14.8) and the combination of phenobarbital and caffeine with other antiepileptic drugs (RR 5.1, CI: 1.5-17.4). Valproate +/- other antiepileptic drugs (odds ratio (OR) = 5.4, p=0.004), valproate monotherapy (OR = 4.0, p=0.03) and valproate + carbamazepine (OR = 8.1, p=0.01) were significantly associated with spina bifida and valproate +/- other antiepileptic drugs (OR = 4.8, p=0.03) and valproate monotherapy (OR = 4.8, p=0.05) with hypospadias. The study shows that polytherapies are more often associated with an increased risk than monotherapies. Valproate and carbamazepine monotherapy show a significantly increased risk of major congenital abnormalities. Valproate monotherapy is especially associated with spina bifida and hypospadias. If valproate is prescribed in monotherapy, keeping the total daily dose as low as possible might diminish the risk of major congenital abnormalities, given the dose-response relationship observed in this studies. Additionally, our study shows that benzodiazepines combined with other antiepileptic drugs, especially valproate and carbamazepine, are associated with an increased risk of major congenital abnormalities and are perhaps better not prescribed in combination with carbamazepine or valproate. There is no information about pregnancy outcome after chronic benzodiazepine monotherapy exposure in maternal epilepsy. Finally, our findings argue against caffeine co-medication in combination with phenobarbital, and a warning is warranted for high caffeine intake from other sources until more is known about a potential teratogenic effect this substance.

In ***Chapter 5.3*** the role of antiepileptic drugs as well as the underlying epilepsy in fetal growth and perinatal outcome were studied. Offspring of mothers with epilepsy using antiepileptic drugs during first trimester of pregnancy had significantly lower weight (difference (d) = 44 g, CI: 11-77), shorter length (d = 0.3 cm, CI: 0.1-0.5) and smaller head circumference (d = 0.6 cm, CI: 0.4-0.8) at birth compared to non-epileptic controls. Valproate monotherapy showed an increased risk of an Apgar scores ≤ 6 at one minute (RR 1.8, CI: 1.1-2.9) and at five minutes (RR 2.5, CI: 1.1-5.3) and valproate polytherapy was associated with a lower weight (d = 93 g, CI: 8-178). Carbamazepine monotherapy was associated with shorter length (d = 0.8 cm, CI: 0.4-1.2), and smaller head circumference (d = 0.8 cm, CI: 0.4-1.2). Carbamazepine polytherapy was associated with lower weight (d = 86 g, CI: 18-154) and smaller head circumference (d = 1.2 cm, CI: 0.7-1.7). Phenobarbital polytherapy was associated with

lower weight (d = 111 g, CI: 50-172) and smaller head circumference (d = 0.7 cm, CI: 0.2-1.2). A smaller head circumference was associated with generalized epilepsy and seizure occurrence during first trimester of pregnancy. When stratifying for type of epilepsy within the mono- or polytherapy regimens, we found an additive effect of the combination generalized epilepsy and valproate, carbamazepine, or phenobarbital on head circumference, and of generalized epilepsy in combination with valproate on weight. The study shows that antiepileptic drugs as well as the underlying epilepsy appear to play an important role in growth and development of the fetus.

Chapter 5.4 describes two siblings with multiple congenital abnormalities and liver cell degeneration after maternal use of carbamazepine during both pregnancies. Carbamazepine has been suggested as the drug of choice in women needing antiepileptic drug treatment during pregnancy, in view of its relatively low teratogenicity. However, this case report supports the concept of carbamazepine-induced teratogenesis in two pregnancies, with almost identical abnormalities. This suggests a gene-environment interaction, and illustrates the need for revised genetic counselling after adverse pregnancy outcome in maternal epilepsy.

Chapter 6 (General discussion) deals with various aspects of this thesis, but mainly focuses on the retrospective population-based study conducted in The Netherlands. The methodological issues of the study are addressed and possible pitfalls are discussed, the clinical implications of the findings in the retrospective study are considered, and suggestions for further research are given.

7.2 Samenvatting

De in dit proefschrift beschreven studies hebben tot doel te bepalen wat de risico's zijn op aangeboren afwijkingen voor kinderen van wie de moeder epilepsie heeft en anti-epileptica gebruikt gedurende de zwangerschap. De studies zijn gericht op risico's op het ontstaan van aangeboren afwijkingen, de foetale groei en Apgar score. Met betrekking tot de anti-epileptica zijn specifieke combinaties van combinaties van geneesmiddelen onderzocht en is de aanwezigheid van dosis-response relaties na gegaan. Ook is de rol van het type epilepsie en de invloed van het optreden van aanvallen gedurende de zwangerschap onderzocht (***hoofdstuk 1***).

In ***hoofdstuk 2*** wordt een overzicht gegeven van eerder verrichte studies, met name met betrekking tot de relatie tussen anti-epileptica en aangeboren afwijkingen. In het algemeen gaat men er van uit dat kinderen van moeders met epilepsie, die gedurende de zwangerschap anti-epileptica gebruiken, een twee tot drie keer verhoogd risico hebben op het krijgen van een aangeboren afwijking. In dit hoofdstuk wordt een opsomming gegeven van aangeboren afwijkingen die frequent bij bepaalde anti-epileptica worden gezien. Verder worden de mogelijkheden van primaire preventie (het voorkomen van aangeboren afwijkingen) besproken, zoals het gebruik van foliumzuur ter preventie van neuraalbuisdefecten, en secundaire preventie, zoals prenatale diagnostiek.

In dit proefschrift worden de resultaten van twee verschillende onderzoeken gepresenteerd. De eerste studie betreft een heranalyse van gegevens uit 5 prospectieve follow-up studies naar zwangerschapsuitkomst bij anti-epileptica gebruik, uitgevoerd in Finland, Duitsland en Nederland tussen 1971 en 1990. De tweede studie betreft een retrospectieve follow-up studie naar zwangerschapsuitkomst bij maternale epilepsie en anti-epileptica gebruik, met gegevens over kinderen geboren in het zuidwesten van Nederland. In ***hoofdstuk 3*** wordt beschreven welke methoden hierbij zijn toegepast en hoe de studies zijn opgebouwd.

Hoofdstuk 4 beschrijft de resultaten van de heranalyse van data van 5 prospectieve follow-up studies naar de rol van anti-epileptica op het ontstaan van aangeboren afwijkingen bij de vrucht. Deze studies zijn uitgevoerd in de periode van 1971-1990. In totaal omvatte de studie 1379 kinderen, waarvan er 1221 blootgesteld waren aan anti-epileptica. Er was een significant verhoogd risico op aangeboren afwijkingen voor kinderen die blootgesteld waren aan anti-epileptica gedurende de zwangerschap (relatief risico (RR) 2.3, 95% betrouwbaarheidsinterval (CI): 1.2-4.7). Het risico was met name

verhoogd voor kinderen die intra-uterien blootgesteld waren aan valproaat (RR 4.9, CI: 1.6-15.0), carbamazepine (RR 4.9, CI: 1.3-18.0). Als specifieke combinaties van anti-epileptica werden vergeleken was het risico op aangeboren afwijkingen duidelijk verhoogd voor de combinatie van phenobarbital met ethosuccimide (RR 9.8, CI: 1.4-67.3) en voor de combinatie van phenytoine, phenobarbital, carbamazepine en valproaat (RR 11.0, CI: 2.1-57.6). Voor valproaat werd een dosis-response relatie gevonden. Kinderen blootgesteld aan meer dan 1000 mg valproaat per dag hadden een significant verhoogd risico op aangeboren afwijkingen (in het bijzonder neuraalbuisdefecten) in vergelijking met kinderen blootgesteld aan minder dan 600 mg valproaat per dag (RR 6.8, CI: 1.4-32.7). De studie heeft enerzijds de risico's van anti-epileptica benadrukt, maar ondanks het feit dat het een heranalyse betrof van gegevens uit vijf studies, bleven de aantallen van verscheidene combinaties van anti-epileptica te klein om hierover uitspraken te kunnen doen over risico's op aangeboren afwijkingen.

Hoofdstuk 5 beschrijft de resultaten van de retrospectieve follow-up studie, met gegevens van kinderen geboren in het zuidwesten van Nederland.
In ***hoofdstuk 5.1*** is de relatie onderzocht tussen verschillende expositie groepen van anti-epileptica (I-IV) (zie hoofdstuk 3) en aangeboren afwijkingen bij de nakomelingen. Kinderen blootgesteld aan anti-epileptica gedurende het eerste trimester van de zwangerschap hadden een duidelijk verhoogd risico op aangeboren afwijkingen (RR 2.6, CI: 1.6-4.1), in vergelijking met de controle populatie. Ook kinderen blootgesteld aan anti-epileptica gedurende zwangerschap, maar alleen gedurende het tweede en/of derde trimester hadden een verhoogd risico op aangeboren afwijkingen. Binnen deze groep was er met name een verhoogd risico voor kinderen van moeders met partiële epilepsie (RR 5.1, CI: 1.5-17.4) en kinderen die gedurende het eerste trimester blootgesteld waren aan epileptische insulten (RR 7.2, CI: 1.6-32.2). Kinderen van moeders met epilepsie die geen anti-epileptica gebruikten gedurende heel de zwangerschap, hadden geen verhoogd risico op aangeboren afwijkingen, in vergelijking met de controle populatie. Dit betekent dat milde vormen van epilepsie, die geen behandeling behoeven, niet gepaard gaan met een verhoogd risico op aangeboren afwijkingen. Deze studie toont aan dat anti-epileptica gebruik gedurende de zwangerschap een teratogeen effect heeft op de vrucht. Bovendien suggereert de studie dat een subpopulatie van vrouwen, die alleen gedurende het tweede en/of derde trimester anti-epileptica gebruikten, een verhoogd risico hebben op het krijgen van een kind met een aangeboren afwijking. Dit geldt met name als de vrouw in kwestie partiële epilepsie heeft of tijdens de zwangerschap epileptische insulten heeft.

In ***hoofdstuk 5.2*** werd de relatie tussen specifieke combinaties van anti-epileptica en aangeboren afwijkingen onderzocht. Voor wat betreft monotherapieën, vonden we een significant verhoogd risico op aangeboren afwijkingen bij het gebruik van carbamazepine (RR 2.6, CI: 1.4-5.0) en valproaat (RR 4.1, CI: 1.9-8.8), met ook in deze studie een significante dosis-response relatie voor valproaat. Kinderen die blootgesteld waren aan meer dan 1000 mg valproaat per dag hadden een significant verhoogd risico op het krijgen van een aangeboren afwijkingen in vergelijking met kinderen die aan minder dan 600 mg valproaat per dag blootgesteld waren (RR 3.9, CI: 1.4-11.1). Het blijkt dus belangrijk om valproaat tijdens de zwangerschap in zo laag mogelijke dosering voor te schrijven. Het risico op aangeboren afwijkingen was niet significant verhoogd voor phenobarbital (RR 2.0, CI: 0.8-5.3) wanneer cafeïne co-medicatie werd uitgesloten. Echter, wanneer cafeïne co-medicatie werd geïncludeerd was er wel een significant verhoogd risico (RR 2.6, CI: 1.1-6.0). Phenytoine was niet geassocieerd met een verhoogd risico op aangeboren afwijkingen (RR 0.5, CI: 0.1-3.4). Betreffende polytherapieën, werd er een verhoogd risico op aangeboren afwijkingen gevonden voor verscheidene combinaties. Benzodiazepines in combinatie met andere anti-epileptica vertoonden een verhoogd risico op aangeboren afwijkingen (RR 4.1, CI: 1.7-10.1). Daarnaast was er een verhoogd risico voor de combinatie van carbamazepine en valproaat (RR 5.0, CI: 1.7-14.8) en de combinatie van phenobarbital met cafeïne en een of meer andere anti-epileptica (RR 5.1, CI: 1.5-17.4). Spina bifida werd met name gevonden bij kinderen blootgesteld aan valproaat met of zonder andere anti-epileptica (odds ratio (OR) 5.4, p=0.004), valproaat monotherapie (OR 4.0, p=0.03) en de combinatie van valproaat en carbamazepine (OR 8.1, p=0.01). Valproaat in combinatie met andere anti-epileptica (OR 4.8, p=0.03) en valproaat monotherapie (OR 4.8, p=0.05) was verder geassocieerd met hypospadie.

De studie toont aan dat polytherapie vaker geassocieerd is met aangeboren afwijkingen dan monotherapie. Bovendien vertonen valproaat en carbamazepine monotherapie een verhoogd risico op aangeboren afwijkingen, waarbij valproaat met name geassocieerd blijkt met spina bifida. Daarnaast duiden de bevindingen van de studie erop dat benzodiazepines in combinatie met ander anti-epileptica, met name valproaat of carbamazepine, een verhoogd risico geven op aangeboren afwijkingen. Er is echter geen informatie voorhanden over het risico op aangeboren afwijkingen bij blootstelling aan benzodiazepines in monotherapie. Ten slotte pleiten de resultaten van onze studie tegen het gebruik van cafeïne als co-medicatie bij phenobarbital. Het effect van cafeïne gebruik tijdens de zwangerschap uit andere bronnen (drank, geneesmiddelen) dient nader te worden onderzocht.

In ***hoofdstuk 5.3*** werd de rol van anti-epileptica, alsmede de rol van het onderliggende type epilepsie vergeleken met betrekking tot foetale groei en Apgar score. Kinderen van moeders met epilepsie, blootgesteld aan anti-epileptica gedurende het eerste trimester van de zwangerschap, hadden een duidelijk lager gewicht (verschil (δ) = 44 g, CI: 11-77), korter lengte (δ = 0.3 cm, CI: 0.1-0.5) en kleinere hoofdomtrek (δ = 0.6, CI: 0.4-0.8) bij de geboorte vergeleken met de controles. Valproaat monotherapie gaf een verhoogd risico op een Apgar score ≤ 6 bij één minuut (RR 1.8, CI: 1.1-2.9) en bij vijf minuten (RR 2.5, CI: 1.1-5.3) bij het kind. Valproaat polytherapie was geassocieerd met een lager geboorte gewicht (δ = 93 g, CI: 8-178). Carbamazepine monotherapie was geassocieerd met een kortere lengte (δ = 0.8 cm, CI: 0.4-1.2) en een kleiner hoofdomtrek (δ = 0.8 cm, CI: 0.4-1.2) bij het kind. Carbamazepine polytherapie was gerelateerd aan een lager geboorte gewicht (δ = 86 g, CI: 18-154) en een kleinere hoofdomtrek (δ = 1.2 cm, CI: 0.7-1.7). Kinderen blootgesteld aan phenobarbital polytherapie hadden een lager geboorte gewicht (δ = 111 g, CI: 50-172) en een kleinere hoofdomtrek (δ = 0.7 cm, CI: 0.2-1.2). Naast therapie is ook het type epilepsie bij de moeder relevant voor de ontwikkeling van het kind. Een laag geboorte gewicht en een kleinere hoofdomtrek waren geassocieerd met gegeneraliseerde epilepsie en een kleinere hoofdomtrek bovendien met het optreden van aanvallen in het eerste trimester van de zwangerschap. Met name gegeneraliseerde epilepsie bij de moeder in combinatie met valproaat, carbamazepine of phenobarbital ging gepaard met een kleinere hoofdomtrek en gegeneraliseerde epilepsie in combinatie met valproaat met een lager geboortegewicht.

In ***hoofdstuk 5.4*** worden twee nakomelingen beschreven met multipele congenitale afwijkingen en levercel degeneratie na carbamazepine gebruik tijdens de zwangerschap. Carbamazepine is vaak het eerste keus anti-epilepticum gedurende de zwangerschap, omdat het als relatief veilig wordt beschouwd. Echter, deze casuïstische bevinding met bijna identiek afwijkingen na carbamazepine blootstelling, suggereert een carbamazepine geïnduceerde teratogenese en een gen-omgeving interactie. Echter, het illustreert tevens het belang van implementatie van mogelijke gen-omgeving interacties in de klinisch-genetische praktijk, als reeds eerder een kind met een afwijking is geboren.

Hoofdstuk 6 (algemene discussie) behandeld diverse aspecten van dit proefschrift, maar richt zich met name op de retrospectieve follow-up studie uitgevoerd in Nederland. Naast de methodologische aspecten en mogelijke valkuilen van de studie

worden de klinische implicaties van de bevindingen besproken. Tenslotte worden suggesties worden gedaan voor toekomstig onderzoek.

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About the author

Bettina Samrén was born on August 12, 1965 in Lund, Sweden. She attended secondary school (Gymnasium ß) at the "Stedelijk Gymnasium" in Haarlem. She attended medical school at the University of Leiden and graduated in 1991. From 1991 to 1992 she worked as a resident at the department of Obstetrics and Gynaecology of the St. Clara Hospital in Rotterdam. In 1992 she started at the departments of Clinical Genetics (head: Prof. dr H. Galjaard) and Epidemiology & Biostatistics (head: Prof. dr A. Hofman) at the Erasmus University Rotterdam, where the work on this thesis was initiated. During this period she received training as an epidemiologist and she received her Master of Science degree in Clinical Epidemiology at the Netherlands Institute of Health Sciences in 1996. Currently she is working at the Municipal Health Survice Rotterdam at the department Eurocat Southwestern Netherlands. She is married to Peter Smak Gregoor and they have a daughter named Anna.